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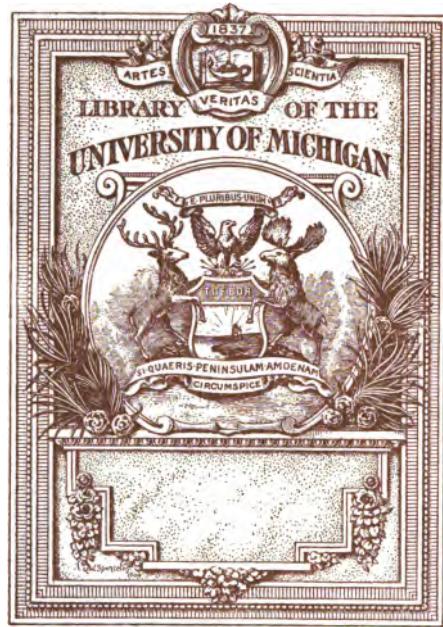
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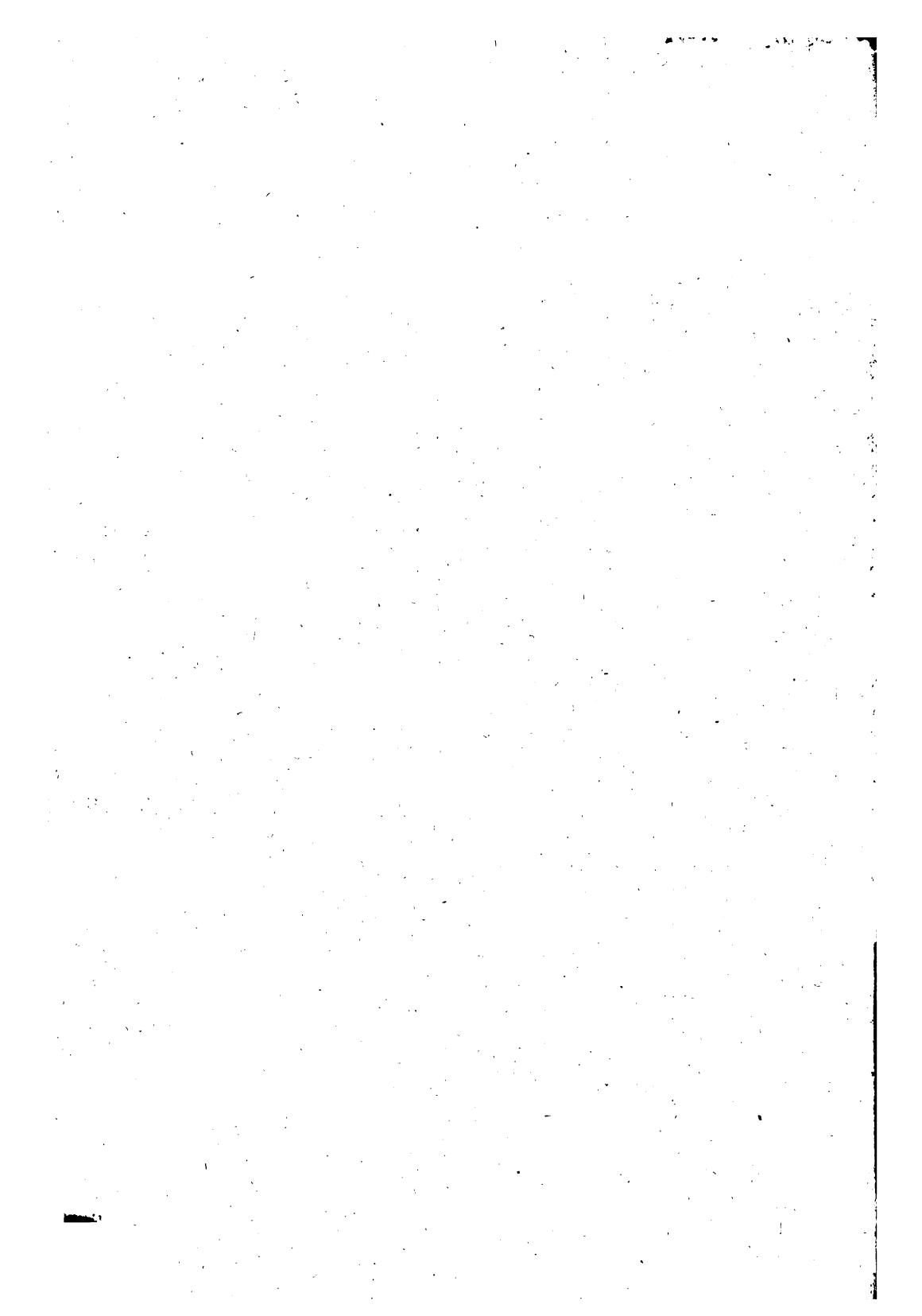


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THE SESQUITERPENES

A MONOGRAPH

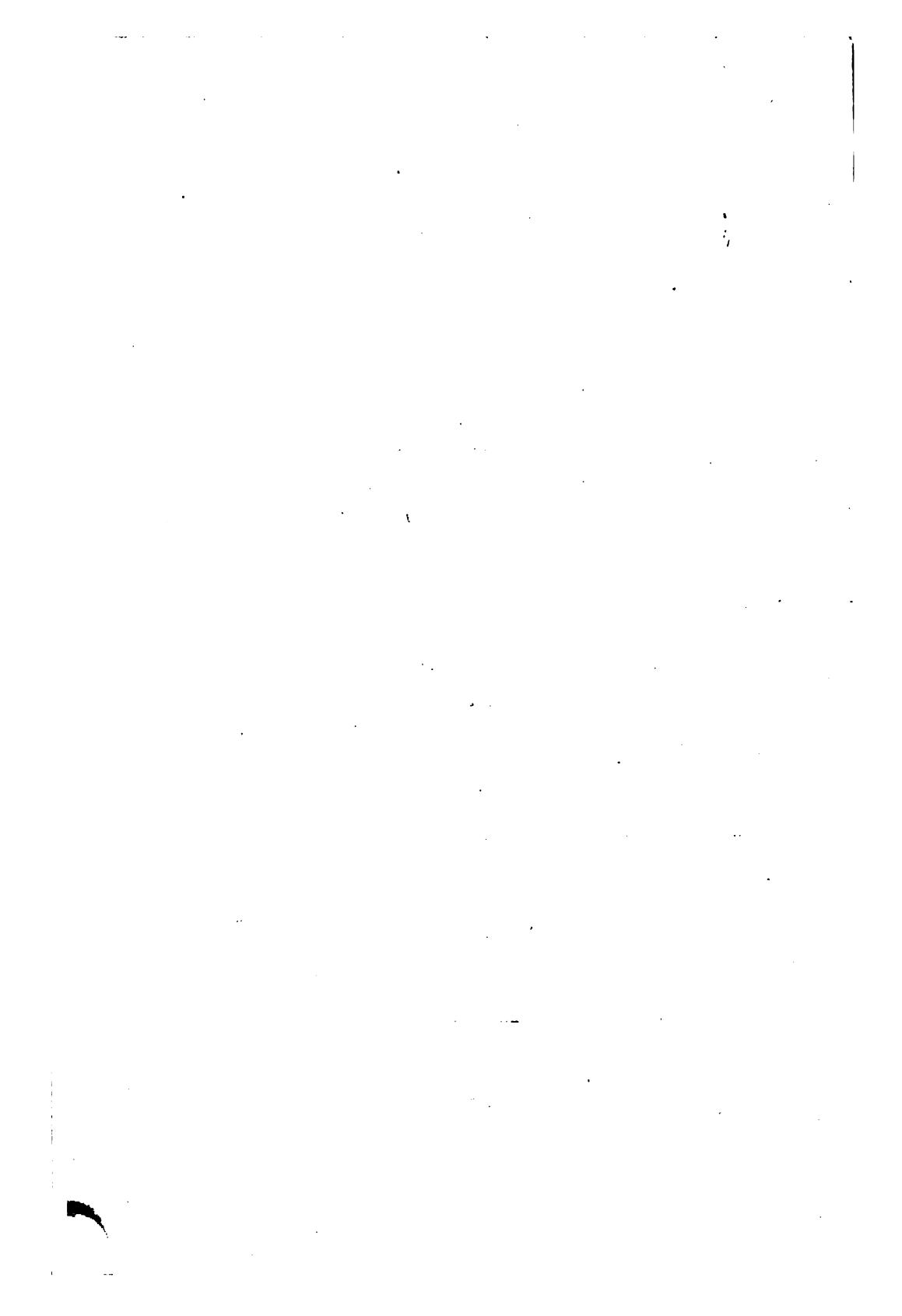
BY

OSWALD SCHREINER

**A THESIS SUBMITTED FOR THE DEGREE OF DOCTOR OF PHILOSOPHY
UNIVERSITY OF WISCONSIN
1902**

Reprinted from the *Pharmaceutical Archives*, vol. 6, pp. 24, 33, 56, 65, 81, 107, 116;
and from the *Pharmaceutical Review*, vol. 22, pp. 60, 101, 131

MADISON
1904



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MADISON

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Wm. H. U.

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The Sesquiterpenes.

A monograph* by *Oswald Schreiner*.

INTRODUCTION.

The volatile oils contain a large number of hydrocarbons of the general formula $(C_5H_8)_x$. This group of hydrocarbons has been designated by the generic word terpenes,¹ although this term is usually more specifically applied to the subgroup $C_{10}H_{16}$. According to the value of x in the general formula, this group of terpenes is classified into

Hemiterpenes, C_5H_8 ,
Terpenes proper, $C_{10}H_{16}$,
Sesquiterpenes, $C_{15}H_{24}$,
Diterpenes, $C_{20}H_{32}$, and higher
Polyterpenes.

Of the hemiterpenes but a single representative has been found in a volatile oil, namely isoprene, in the oil obtained by destructive distillation of caoutchouc or gutta percha. The terpenes proper and sesquiterpenes are among the principal constituents of the volatile oils. The diterpenes and higher polyterpenes are more rarely found and but little studied.

The chemical study of the terpenes proper and of allied oxygen derivatives has opened up a fruitful field of research and made possible the rapid development of the volatile oil industry. Not only has this industry been placed on a scientific and permanent basis, but pure science as well has profited greatly, for some of the most important theories in organic and physical chemistry have sprung out of, or have found a most fruitful field in the study of this class of hydrocarbons and their derivatives.

The first chemical derivative of a terpene was prepared by Kindt in 1802 by the action of hydrochloric acid on turpentine oil. The preparation of hydrochlorides remained for many years the only

* Thesis submitted for the doctor's degree, University of Wisconsin, June, 1902.

¹ This term appears to have been introduced by Kekulé in 1866 (from German Terpentin) and comprised all natural hydrocarbons $C_{10}H_{16}$. Later it was made to comprise all hydrocarbons, natural and artificial $(C_5H_8)_x$. It should not be confounded with the modern modified usage suggested by v. Baeyer in accordance with the Geneva Congress nomenclature. According to his suggestion tetrahydrocymenes, $C_{10}H_{16}$, are "terpenes," whereas dihydrocymenes, $C_{10}H_{16}$ (comprising but one of the numerous possible subgroups of terpenes, according to the oldest conception of the term), are to be designated terpadienes, because they have two double bonds, hence di-enes.

means for the characterization of the terpenes. The results were, however, so mislending, due to the isomerization which this acid often induces, that in 1884, when Wallach began his researches, the literature of the terpenes was in a chaotic condition. The pioneer researches of this investigator, together with the work of his co-laborers and followers, has brought order out of chaos.

The derivatives which, more than any others, have made the characterization and identification of the terpenes possible, have been the addition compounds with nitrosyl chloride and the oxides of nitrogen: the nitrosochlorides, nitrosates, nitrosites and nitroso-nitro compounds. With one exception, these nitroso compounds are very reactive, especially with organic bases, giving rise to nitrolamines which are well crystallized compounds of sharp melting points. By the preparation of these derivatives most of the terpenes can now be readily identified.

While the terpenes have been so well characterized that the determination of their different modifications offers no particular difficulty, and the investigation of these hydrocarbons is being continued along sure and well beaten paths, the sesquiterpenes until a very recent date have resisted investigation along parallel lines. The conditions for the study of the hydrocarbons of the formula $C_{15}H_{24}$ are exceedingly unfavorable. The sesquiterpenes are thick, easily resinifying liquids with a boiling point between 250° and 280° ; in short, their properties are such that they do not invite investigation.

In 1887 Wallach² declared his intention to study the sesquiterpenes along lines parallel to those which had proven so successful in the investigation of the terpenes. He reports at the time on the dihydrochloride of cadinene and on the pure regenerated cadinene. In 1892 he made a second report,³ in which he characterizes the sesquiterpene of clove and copaiba balsam oils, giving it the name of caryophyllene. Among the characteristic derivatives prepared was a nitrosochloride. Several other sesquiterpenes are considered but not characterized. Two years later Wallach⁴ published some further notes on the sesquiterpenes, among them a method for the preparation of caryophyllene nitrosate. This is his last contribution to the subject, as the methods which he had used with so much success in the study of the terpenes seemed to all but fail in the study of the refractory

² Ann., 238, p. 82.

³ Ann., 271, p. 285.

⁴ Ann., 279, p. 391.

sesquiterpenes. At the beginning of his last communication he says: "Um eine sichere Unterscheidung der Sesquiterpene zu ermöglichen, die Isomerie-Verhältnisse innerhalb der Körperklasse klarzustellen und damit eine sichere Grundlage für Arbeiten über die Constitutionen dieser Verbindungen zu schaffen, beabsichtigte ich in ähnlicher Weise systematisch vorzugehen, wie ich es bei der Gruppe der Terpene gethan habe. Nachdem ich mich davon überzeugen musste, wie undankbar eine solche Arbeit ist, verzichte ich wenigstens auf die systematische Weiterführung und will vorläufig nur noch einige Erfahrungen mittheilen."

Chapman's⁵ experience with the nitroso derivatives of humulene seemed to indicate that the work was not altogether hopeless. Four years after Wallach made his last communication on the sesquiterpenes, the study of this group of hydrocarbons was begun in this laboratory and has been continued steadily since 1897. The results have been published from time to time in a series of articles entitled "The Characterization and Classification of the Sesquiterpenes," as follows:

1. True and bis-nitroso addition products of caryophyllene, by Oswald Schreiner and Charlotte F. James. Reported by Edward Kremers.⁶
2. Nitroso derivatives of caryophyllene and cadinene, by Oswald Schreiner and Edward Kremers.⁷
3. Caryophyllene and zingiberene derivatives, by Oswald Schreiner and Edward Kremers.⁸
4. Zingiberene and its derivatives, by Oswald Schreiner and Edward Kremers.⁹

The results thus far obtained seem to show that the field of the sesquiterpenes is not so discouraging as Wallach had supposed. By the modification of old methods or the application of new ones, gratifying results have been obtained; in fact the outlook has assumed rather encouraging aspects.*

The first points of attack should naturally be the preparation of characteristic derivatives, which will allow us to separate, distinguish and identify the individual sesquiterpenes, and then to classify them.

⁵ Journ. Chem. Soc., 67, pp. 54 & 780.

⁶ Pharm. Archives, 1, p. 209.

⁷ Pharm. Archives, 2, p. 273; Proc. Am. Pharm. Assoc., 1899, p. 158.

⁸ Pharm. Archives, 4, p. 61.

⁹ Pharm. Archives, 4, p. 155; Proc. Am. Pharm. Assoc., 49, p. 329.

* The statement recently made by Gadamer (Arch. d. Pharm., 241, p. 22) viz. that "little more than the physical constants" of the sesquiterpenes are known, is not based on facts. Dr. Gadamer's study of the literature evidently was very superficial for he not even copied the names of the authors correctly.

The characterization of several of the large number of known sesquiterpenes has been accomplished. Like investigation of those not yet characterized will, no doubt, reduce materially the still considerable number of supposedly different hydrocarbons. A system for their classification is also suggested in the body of this report. This system of classification does not only include the sesquiterpenes at present known and characterized, but being based broadly on the best principles of classification of hydrocarbons in general, it will include all the numerous possible compounds of the formula $C_{15}H_{24}$.

Only after the characterization of the numerous isomers is accomplished will it be possible to study successfully the relation of one sesquiterpene to another, the relation of these hydrocarbons to their oxygenated derivatives, and the problem of their constitution.

GENERAL PART.

I. The Position of the Sesquiterpenes in the Various Systems of Classification of Terpenes at large (C_5H_8) x .

Until quite recently the hydrocarbons of the formula $(C_5H_8)_x$ were identified and classified on the basis of their physical characteristics alone. Such a system inevitably had to lead to endless confusion. The hydrocarbon was usually named according to the plant from the volatile oil of which it had been isolated, or simply after the volatile oil itself. Thus, for instance, limonene was differently named, and also considered as a different compound, according to the source from which it was obtained. The limonene in lemon oil was considered as an isomer of that in orange oil, that in the oil of *Citrus bigaradia* as an isomer of that in the oil of *Citrus lumia*, and isomeric with all these was the limonene in caraway oil, the carvene. Thus we find in literature as many as ten synonyms for limonene, and as many as twenty synonyms for dipentene, the optically inactive modification of limonene. Pinene, as it occurs in the various turpentine oils; camphene; dipentene, obtained from dipentene dihydrochloride, the "camphre de citron;" caoutchene, etc., were also considered as isomeric with these. This historical kind of quasi-isomerism, based on the source of the isolated hydrocarbons, might be termed genetic isomerism.

This large group of supposedly different hydrocarbons was due to the fact that they are very often accompanied in the volatile oils by oxygenated constituents, which are not readily separated from the

hydrocarbons by fractional distillation. In other cases, two or more hydrocarbons are simultaneously present in the oil, and the resulting hydrocarbon fraction was often considered a distinct hydrocarbon. Thus it happened that fractions were obtained which differed in odor and physical characteristics from the hydrocarbons then known, and were at once given specific names and considered as isomers of the others.

For a long time no distinction was drawn between these two kinds of isomerism, the genetic, as we have called it, and the chemical; not even when the study of the hydrocarbons revealed that the turpentine oils behaved quite differently from the oils of the citrus species toward hydrochloric acid and other chemical agents. Gladstone (1864) was the first to question this so-called genetic isomerism and to express the idea that the hydrocarbons of the different citrus species were not isomeric but identical. Although his conclusions were not always correct, he nevertheless produced some order in this chaotic field by his classification based on physical properties. It was, however, not until the work of Tilden and especially that of Wallach supplied characteristic chemical compounds that the different terpene groups could be identified.

The chemical characterization and classification of the terpenes proper, based on the work of Wallach and others, has cleared up the needless complexity of names caused by a style of nomenclature based largely on the botanical or other source of the hydrocarbon.

In the field of the sesquiterpenes much more remains to be done. If the names given to hydrocarbons $C_{15}H_{24}$ from different oils are to be regarded as standing for as many sesquiterpenes, there are at present more than sixty of these compounds. The confusion accompanying this genetic style of nomenclature will, no doubt, be removed with increasing knowledge of these substances.

The sesquiterpene of pepper oil has already shown itself to be identical with caryophyllene. Further work will doubtless show many of these "genetic" isomers to be identical with known sesquiterpenes, and the total number be thus materially reduced.

A classification of the hydrocarbons of the formula $(C_5H_8)_x$ on a physico-chemical basis seems first to have been attempted by Schödler.¹⁰ According to this rather popular writer, the "volatile oils" were divided into three orders of *camphenes*.

¹⁰ See Fr. Gruenling, Dissert., p. 11, Strassburg, 1879.

Camphenes of the I. order. These were the natural hydrocarbons.

They differed from the members of the following orders in possessing optical activity.

Camphenes of the II. order, designated as *campherenes*. These were the isomeric modifications resulting by simple chemical reactions from the hydrocarbons of the I. order. They and their compounds were optically inactive.

Camphenes of the III. order, designated as *camphilenes*. These were the isomeric compounds which resulted by more complex reactions from the foregoing. They were also inactive.

Concerning the term camphene it may be of interest to add that Soubeiran and Capitaine¹¹ in 1840 made the following statement in regard to the nomenclature used by them: "Camphène est pour nous le nom générique qui réunit toutes les espèces C_5H_8 . Nous appliquons la terminaison ène à toutes celles de ces huiles hydrocarbonées qui forment une combinaison solide avec l'acide hydrochlorique. Nous employons la terminaison ilène pour celles qui donnent un camphre liquide."

Gerhardt¹² in 1846, following the system of Gmelin, divided all organic compounds into families according to the number of carbon atoms in the compound. The hydrocarbons of the general formula $(C_5H_8)_x$ were classified according to their boiling points and vapor density as follows:

Camphenes, belonging to the tenth family, $C_{10}H_{16} = 2$ volumes of vapor and boiling at about 160° .

Paracamphenes, belonging to the fifteenth family, $C_{15}H_{24} = 2$ volumes of vapor and boiling at about 260° .

Metacamphenes, belonging to the twentieth family, $C_{20}H_{32} = 2$ volumes of vapor and boiling at about 310° .

Berthelot¹³ in 1860 showed these systems of classification to be entirely inadequate. Having more particularly studied the optical relations of the terpenes, he distinguished between those occurring in nature and those obtained from the latter by a number of reactions. His classification was as follows:

- I. Natural hydrocarbons; *terebenthenes*.¹⁴
- II. Artificial hydrocarbons obtained from the natural hydrocarbons,

¹¹ Journ. de Pharm., 26, p. 1.

¹² Grundr. d. org. Chem., 2, pp. 242, 413, 502.

¹³ Chim. org. fond. s.l. Synthèse, 2, p. 781.

¹⁴ Camphenes of the I. order (Schödler).

1. By heat;
2. By the action of acids or similar agents; *terebenes*.¹⁵
3. By the formation of chemical derivatives, such as hydrochlorides and hydrates, and subsequent generation of the hydrocarbon. The members of this group were differentiated into
 - a. *Camphenes*.¹⁶ The crystallized monochlorhydrate gives by careful decomposition camphene, which crystallizes, is optically active, and yields with hydrochloric acid the original chlorhydrate.
 - b. *Camphilenes*. The liquid monochlorhydrate contains a hydrocarbon camphilene; it is liquid, but is separated unchanged only with difficulty.
 - c. *Terpilenes*. These are obtained by careful decomposition of the dichlorhydrates; they are, like the dichlorhydrates themselves, optically inactive.

The polymers of the terebenthenes were designated as *paraterbenthenes*,¹⁷ polymers of the *pyrolenes* as *metapyrolenes*.

Later, in 1862, Berthelot¹⁸ gave the following classification: "In accordance with known facts, the hydrocarbon $C_{10}H_{16}$ —e. g. terebenthene—may be regarded as the starting point of two series:

1. Of a monatomic or camphol¹⁹ series (monohydrochlorides or chlorine esters of camphol, $C_{10}H_{17}Cl$; camphene, $C_{10}H_{16}$; camphol alcohols, $C_{10}H_{18}$);
2. Of a diatomic or terpil series (dihydrochlorides, $C_{10}H_{18}Cl_2$; terpilene, $C_{10}H_{16}$; hydrate, $C_{10}H_{20}O_2$).

Each of these two series constitutes a larger group, which can be divided into secondary series, the parallel and isomeric members of which occur in twos; each has as type an inactive hydrocarbon: namely camphene in the first group; terpilene in the second."

The next important classification is that by Gladstone²⁰ in 1864. Although based on physical properties alone, this system is in its main lines similar to the later chemical system of classification. He divided the hydrocarbons $(C_5H_8)_x$ into compounds, I. $C_{10}H_{16}$; II. $C_{15}H_{24}$; III. $C_{20}H_{32}$. The hydrocarbons $C_{10}H_{16}$ were subdivided into two further groups, as is seen from the following:

¹⁵ Camphenes of the II. order; camphenenes (Schödler).

¹⁶ Camphenes of the III. order; camphilenes (Schödler).

¹⁷ Paracamphenes (Gerhardt).

¹⁸ Compt. rend., 55, p. 496, 544; Ann., Suppl. 2, p. 235.

¹⁹ Name applied by Berthelot to borneol.

²⁰ Journ. Chem. Soc., 17, p. 1.

- I. (a) Sp. gr. = 0.846; boiling point about 178°; formula C₁₀H₁₆.
 (b) Sp. gr. = 0.85+; boiling point about 160°; formula C₁₀H₁₆.

II. Sp. gr. = 0.90+ to 0.92+; boiling point 250—260°; formula C₁₅H₂₄.

III. Colophene; boiling point about 315°; formula C₂₀H₃₂.

To group I a belong the hydrocarbons of the citrus species, which he considers identical rather than isomeric. Group I b consists of the hydrocarbons of the turpentine oils, etc.

About this time the word *terpene* was introduced, evidently by Kekulé. In his *Lehrbuch der organischen Chemie* (1866), II, p. 437, he says, “—das Terpentinöl und die zahlreichen mit ihm isomeren Kohlenwasserstoffe, welche im Allgemeinen als Terpene bezeichnet werden mögen.” The use of the word *terpene* in a larger sense is of a later date.

In a second communication made by Gladstone²¹ in 1871, he makes a more detailed comparison of the physical properties of the respective groups. The table given to show these group differences is of interest in this connection, and is herewith reproduced.

	10-Carbon Group.	15-Carbon Group.	Colophene.
Formula.....	C ₁₀ H ₁₆	C ₁₅ H ₂₄	C ₂₀ H ₃₂
Vapor density.....	4.7	7.1	—
Character of liquid.....	Liquid	Viscid	Very viscid
Sp. gr. at 20°.....	0.846—0.880	0.904—0.927	0.939
Refractive index for A, at 20°	1.457—1.467	1.488—1.497	1.5084
Dispersion.....	About 0.027	About 0.029	0.031
Sensitiveness*.....	About 48	About 43	41
Boiling point.....	160—176°	249—260°	315°
Action of sulphuric acid.....	Polymerizes	Doubtful	None
Solubility in aqueous alcohol	Freely soluble	Sparingly soluble	Insoluble
Combination with HCl.....	{ C ₁₀ H ₁₆ 2HCl } and C ₁₀ H ₁₆ HCl }	{ C ₁₅ H ₂₄ 2HCl } and in smaller proportions	Very small quantity

Gladstone remarks on the table as follows: “It will be evident that the middle or fifteen-carbon group is intermediate in all its properties, and that these groups do not pass by insensible gradations into one another, but are separated by strongly marked divisions. There is no difference in specific refractive energy, and the various

²¹ Journ. Chem. Soc., 25, p. 1; Pharm. Journ., 31, p. 704.
 * This refers to expansibility by heat.

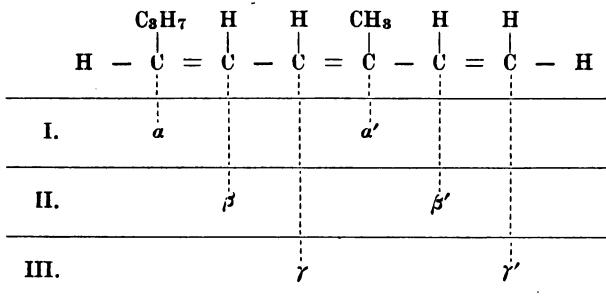
members of the ten- and fifteen-carbon groups at least have powerful odors, and rotate the plane of polarization strongly, sometimes in one, sometimes in the other direction."

Based on the different properties of the nitroso compounds, Tilden²² in 1877 divided the terpenes, C₁₀H₁₆, into two groups, as follows:

1. Turpentine group. Boiling point 156–160°; melting point of nitroso derivatives 124°; they form solid crystalline hydrated terpin C₁₀H₂₀O₂.H₂O.
2. Orange group. Boiling point 174–176°; melting point of nitroso derivatives 71°; form (by Wigger's process) no solid crystalline terpin hydrate.²³

Of the individual members of the group Tilden says: "The liquids included in each group are allotropic modifications of the same hydrocarbon, distinguished one from another by their various rotatory action on the polarized ray."

In 1878 Tilden²⁴ set up the following formula to explain the constitution of the terpenes, which is of interest as he proposes a classification of the terpenes, C₁₀H₁₆, in connection with it:



According to the boiling points, specific gravity, and the action of certain agents, especially nitrosyl chloride, he divides the terpenes into the three classes indicated above:

²² Pharm. Journ., 37, p. 191.

²³ This statement is not correct. Both dipentene and limonene produce terpin hydrate. Comp. Flückiger, Arch. d. Pharm., 222, p. 862; also Kremers, Ann. Chem. Journ., 15, p. 695.

²⁴ Ber., 11, p. 152.

I. Propyl and methyl groups connected with the carbon atoms α and α' .

II. The groups connected with β and β' .

III. The groups connected with γ and γ' .

Armstrong and Wright are, however, of the opinion that this explanation is insufficient, and that the camphenes doubtless form a fourth class.

In 1879 Tilden²⁵ again distinguished between the low boiling (turpentine group) and the high boiling terpenes (orange group). The former combine with one molecule, the latter with two molecules of hydrochloric acid.

In 1886 Gladstone²⁶ reports on the refraction and dispersion equivalents of the volatile oils. Based on these additional physical constants, he continues his classification of these hydrocarbons. He says: "It is now generally accepted that the isomeric oils of the formula $C_{10}H_{16}$ fall into two groups—the terpenes and the citrenes, or isoterpenes. These two groups, together with the cedrenes,²⁷ $C_{15}H_{24}$, differ in boiling point, specific gravity, and rotatory power, and also in specific refractive and dispersive energy." Based on the optical properties, he comes to the following "speculative" conclusion:²⁸ "That the citrenes differ from the terpenes by containing a second pair of doubly-linked carbon atoms, and that the double-linking of this second pair is also analogous to that of the olefines."

In this statement, based on purely physical properties, we find the germ of the later physico-chemical classification. Nor is the recognition of this difference in the constitution of the "citrenes" and "terpenes" entirely due to Gladstone. Even the earliest investigators in this field voiced this difference, not indeed in the term of double bonds, for the usage of this term does not date back so far. Thus we find distinction made between the *double saturation capacity* of limonene and the *single saturation capacity* of pinene.²⁹ Berthelot³⁰

²⁵ Ber., 12, p. 1181.

²⁶ Journ. Chem. Soc., 49, p. 611.

²⁷ This term appears to have been introduced by Beckett and Wright (Journ. Chem. Soc., [8], 1, p. 6) in 1876. They speak of the hydrocarbons $C_{15}H_{24}$ as "sesquipolymerides of terpenes, or cedrenes, as they may be economically termed."

²⁸ Chem. News, 54, p. 323.

²⁹ Soubiran and Capitaine.

³⁰ Compt. rend., 55, pp. 495 and 544; Ann., Suppl. 2, p. 286.

is perhaps the only one who, at least for a time, considered this distinction as unimportant. This same saturation idea is emphasized in Tilden's⁸¹ work above cited. The modern classification based on structural differences may, therefore, be said to have had a gradual development.

Wallach⁸² in 1885 proposed the following classification for the hydrocarbons of the formula (C_5H_8) x :

- A. Hemiterpenes or pentenes of the formula C_5H_8 .
- B. Terpenes proper, $C_{10}H_{16}$. This class was subdivided into the groups: 1) pinene, 2) camphene, 3) limonene, 4) dipentene, etc.
- C. Polyterpenes (C_5H_8) x .
 - 1. Sesquiterpenes⁸³ or tripentenes, $C_{15}H_{24}$.
 - 2. Diterpenes or tetrapentenes, $C_{20}H_{32}$.
 - 3. Polyterpenes, ($C_{10}H_{16}$) x .

Brühl⁸⁴ in 1888 extended his researches on the influence of the single and double linkage of carbon atoms on the refraction of light to the terpenes. He found that the terpenes proper could be classified according to the number of double bonds in the compound as follows:

- 1. Those containing two double bonds.
- 2. " " one " "
- 3. " " no " "

Of the sesquiterpenes Brühl says: "Ueber die Natur dieser Körper ist bisher nichts weiter bekannt, als dass die Mehrzahl derselben nach der Saturationsformel $C_{10}H_{24}|=2$ zusammengesetzt ist. Möglicherweise existiren auch Sättigungsisomere, z. B. $C_{15}H_{24}|=$, doch weiss man darüber noch nichts Bestimmtes. Eine durch Thatssachen begründbare Ansicht über die Structurverhältnisse der Sesquiterpene lässt sich daher zur Zeit nicht vorbringen."

The classification of Wallach and of Brühl underwent slight modification with the discovery and study of new terpenes. The insufficiency of this system was, however, especially emphasized by the discovery by Semmler of a chain compound $C_{10}H_{16}$, which he called an olefinic terpene.

In the earlier classifications the sesquiterpenes were left entirely out of consideration, and indeed beyond the classification into com-

⁸¹ Ber., 12, p. 1181.

⁸² Ann., 227, p. 800.

⁸³ This appears to be the earliest use of the term.

⁸⁴ Ber., 21, p. 145.

pounds, $C_{10}H_{16}$, $C_{15}H_{24}$ and $C_{20}H_{32}$, they were scarcely considered. The terpenes proper were offering so much difficulty at the time that the study of the higher boiling viscous sesquiterpenes was considered as a hopeless chemical problem, and, as is usually done in such cases, they were entirely omitted from any attempt at classification beyond that necessitated by differences in molecular weight.

In 1892 Wallach⁸⁵ suggested a classification of the sesquiterpenes along lines similar to those of the terpenes. He divided them into two groups:

- I. Those containing two double bonds.
- II. Those containing one double bond.

At that time there were only two sesquiterpenes which were characterized, and these only partially. Cadinene belonged undoubtedly to the group containing two double bonds, as its molecular refraction and dihydrochloride indicated. Although the molecular refraction of caryophyllene, the other characterized sesquiterpene, showed two double bonds, Wallach was of the opinion that perhaps it contained only one, because the monohydrate was a saturated compound. By dehydration this monohydrate did not yield caryophyllene, but a sesquiterpene containing only one double bond, and called by Wallach clovene.

As will be pointed out in the following chapters, a more extensive system of classification will be necessary for the sesquiterpenes, for no system of classification which is based solely on the insufficient data of imperfectly known substances will suffice for any length of time. A classification of the group of hydrocarbons $C_{10}H_{16}$ that is to prove more than ephemerally useful must be based broadly on the best classification of hydrocarbons in general. This applies to the sesquiterpenes as well as to the terpenes proper. The classification of the terpenes was developed historically for a threefold purpose. First of all, to show the imperfections of any system that contents itself with actual facts and ignores all possibilities; secondly, because the historical classification of the sesquiterpenes naturally developed along lines laid down for the terpenes proper; and thirdly, because the principles underlying a broadly rational classification of the sesquiterpenes are the same as those upon which the classification of the terpenes proper is based, only the conditions are more complex.

⁸⁵ Ann., 271, p. 296.

II. The Position of the Sesquiterpenes in the Modern Rational System of Classification of Hydrocarbons.

If the group of sesquiterpenes be considered apart from any connection with terpenes at large, but simply as isomeric hydrocarbons of the formula $C_{15}H_{24}$, it will readily be seen that in the general system of classification they must come under the formula of saturation C_nH_{2n-6} .

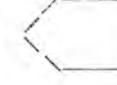
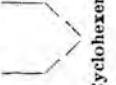
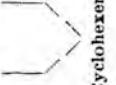
This formula of saturation reveals that, since there are eight unsaturated carbon affinities, there must be four double bonds or their equivalents in the molecule. If the eight hydrogen atoms had been abstracted from a saturated chain compound, $C_{15}H_{32}$, in four pairs from as many pairs of neighboring carbon atoms, a double bond would be introduced between each set of carbon atoms thus treated. In this case the general chain-like character of the hydrocarbon would remain unaffected. If, however, two of the hydrogen atoms had been removed from carbon atoms not neighboring, these two free affinities would unite and produce a cycle instead of a double bond. A cycle, therefore, is the structural equivalent of a double bond. Applying this principle to the formula of saturation C_nH_{2n-6} , it becomes evident that the following groups of compounds must result:

- I. Chain compounds with four double bonds.
- II. Monocyclic compounds with three double bonds.
- III. Dicyclic compounds with two double bonds.
- IV. Tricyclic compounds with one double bond.
- V. Tetracyclic compounds with no double bond.

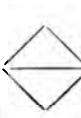
Although it will be evident that in each one of these groups the number of isomeric forms will be great, it may, nevertheless, be advisable here to point out some of the possibilities of the numerous isomeric forms.

Thus, for instance, in the first group the basal chain, i. e. the genus according to the Geneva Congress nomenclature, first of all comes in for numerous isomeric forms according to the number and position of the double bonds. Numerous isomeric forms of position are further indicated by the position of the side chain or side chains. Again some of the side chains, from propyl upward, may exist in two or more isomeric forms. Finally one or all of the double bonds may be in the side chains, and their position would again bring about a variety of isomeric forms.

I. Monocyclic Group.

Derivatives of cycle of three members.	Derivatives of cycle of four members.	Derivatives of five members.	Derivatives of six members.
	 Cyclotetraene.	 Cyclopentane.	 Cyclohexane. Etc.
	 Cyclopentene.	 Cyclohexene. Etc.	 Cycloheptadiene.  Cyclohexadiene. Etc.
	 Cyclopentene.	 Cyclohexene. Etc.	 Cycloheptadiene.  Cyclohexadiene. Etc.

II. Diecyclic Group.

Derivatives of dicyclic of four members.	Derivatives of dicyclic of five members.	Derivatives of dicyclic of six members.	Derivatives of dicyclic of seven members.	Derivatives of dicyclic of eight members.	Derivatives of dicyclic of nine members.	Derivatives of dicyclic of ten members.
	 	 	 	 	 	 
Dicyclotetraene.	Dicyclotetraene. Dicyclotetrene.	Dicyclopentane. Dicyclopentene.	Dicyclohexane. Dicyclohexene.	Dicycloheptane. Dicycloheptene.	Dicyclooctane. Dicyclooctene.	Dicyclononane. Dicyclononene.
Dicyclotetraene.	Dicyclotetraene.	Dicyclopentane.	Dicyclopentane.	Dicyclohexane.	Dicyclooctane.	Dicyclononane.
				Dicyclohexadiene.	Dicyclooctadiene.	Dicyclononadiene.
				Dicyclopentadiene.	Dicycloheptadiene.	Dicyclononadiene.
					Dicyclooctadiene.	Dicyclononadiene.
					Dicyclooctadiene.	Dicyclononadiene.

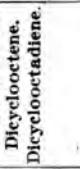


Dicyclohexane,
Dicyclooctene,
Dicyclononene,
Dicyclononadiene.



Dicyclooctane.
Dicyclooctene.
Dicyclooctadiene.

Dicyclononane,
Dicyclononene,
Dicyclononadiene.



Dicyclononane,
Dicyclononene,
Dicyclononadiene.

This also applies in the main to the other groups, but here the cyclic nature of the compound adds a new factor.

As demonstrated in Chart I, the monocyclic group allows of a further subdivision into what might be called *nuclear types* as follows:

Type 1: Three carbon atoms in the cycle.

" 2: Four " " "

" 3: Five " " "

" 4: Six " " "

It is hardly necessary to go beyond the six-membered cycle, as nearly all known compounds fall within this limit. Each of these nuclear types may be further divided according to the number of double bonds in the cycle, as is shown in the chart.

With the introduction of the side chains, the position of the double bond or bonds with reference to the chain or chains must be considered and the number of possibilities is greatly increased. If the isomerism of the side chains is also considered, the possibilities become still greater.

The second chart shows the dicyclic group, divided into nuclear types, and the subdivisions of these. In this group the isomerism becomes more complex, and for this reason the types have been indicated rather than filled out. In this chart the two cycles are represented as being connected by two carbon atoms, thus forming a compound nucleus. It is of course possible that they be connected by only one carbon atom, and they may even be connected by an intervening chain of carbon atoms.

With the tricyclic and tetracyclic groups the isomerism in the nuclear types becomes quite complex, but it must be remembered that as the isomerism of the nucleus increases, the possible number of isomers due to the side chains continually decreases so that the total number of isomers in a group does not necessarily increase with the number of the cycles.

The foregoing considerations give us a very extensive system of classification for the sesquiterpenes. Based on the formula of saturation, it includes every possible compound of the formula $C_{15}H_{24}$, from a tetracyclic to a chain compound, and every possible nuclear structure. Although the number of theoretically possible isomers of the sesquiterpenes is exceedingly large, amounting to many thousands, the number of these compounds which will concern chemists

for a long time to come is far less. At present we can only hope to classify the sesquiterpenes into groups of chain, monocyclic, dicyclic, tricyclic and tetracyclic compounds. In order to accomplish even this much, the sesquiterpenes must first be well characterized and identified. It is this phase of the work that is now carried on in this laboratory. This accomplished, the compounds may be more closely studied and their structure determined if possible, thus assigning each member of the group to its proper nuclear type.

III. Classification and Comparison of the Better Known Sesquiterpenes and Discussion of Possible Constitution and Synthesis.

The theoretical discussion of the possibilities of the formula $C_{15}H_{24}$ in the preceding chapter shows that the sesquiterpenes offer a large field for chemical research. Although the knowledge of this class of hydrocarbons is still in its infancy, the experimental facts already indicate the probable existence of representatives of four out of the five possible groups. The apparent existence of isomers in this group of compounds, varying from tricyclic to chain compounds, offers a field for investigation which for breadth is possibly not duplicated by any other class of isomeric hydrocarbons.

In the accompanying table those sesquiterpenes of which both the specific gravity and index of refraction have been determined, so

Group.	Sesquiterpene.	'Sp. gr.	Molecular refraction.	
			Found	Calculated
Tetracyclic.				62.74
Tricyclic.	Cedrene.....	0.936	64.13	64.45
	Clovene.....	0.930	64.77	
	Patchoulene.....	0.939	64.02	
Dicyclic.	Araliene.....	0.909	65.82	66.15
	Cadinene.....	0.918	65.93	
	Caparrapene.....	0.902	65.85	
	Caryophyllene.....	0.903	66.27	
	Galipene.....	0.912	66.22	
	Guajene.....	0.910	65.92	
	Humulene.....	0.898	66.93	
	Rhodiene.....			
	α -Santalene.....	0.913	*	
	β -Santalene.....	0.914	*	
Monocyclic.	Bisabolene.....	0.891	67.35	67.86
	Zingiberene.....	0.873	67.87	
Chain.	fr. Citronella oil.....	0.864	71.43	69.57

as to make the calculation of the molecular refraction possible, are given. The santalenes are also included because their chemical properties and specific gravity indicate the group to which they belong. It is to be remembered that in only a few cases has the sesquiterpene under consideration been of reasonable purity, and the physical constants are therefore not absolutely accurate. Moreover, some of the sesquiterpenes given, may in future be found to be identical with one or the other of the better characterized sesquiterpenes.

The arrangement of the table shows at once that the sesquiterpenes fall into groups, both as to their specific gravities and especially their molecular refractions. The results are clearly in harmony with the Lundolt-Brühl theory of the influence of double bonds on the molecular refraction, a marked deviation from the exact quantitative relation being found only in the case of the sesquiterpene from citronella oil of rather uncertain purity.

In this classification the specific gravity is likewise of great importance, the rule being that the more unsaturated the sesquiterpene, the lower its specific gravity. It is thus seen that the specific gravity alone will at least indicate the probable class to which the sesquiterpene belongs.

Another property that seems to vary with the constitution of the sesquiterpenes, is the dispersion, although the data at hand are too meagre to more than merely indicate a difference in dispersive power.

The position of some of these better known sesquiterpenes in this system of classification may now be considered.

The *tetracyclic* group. The members of this group, containing no double bonds, will be difficult to attack experimentally at the present state of our knowledge. They cannot form halogen or hydrohalogen addition products, nor yield nitroso addition products without suffering a break in the cycle. They may yield substitution products and thus be brought into the realm of experimental chemical research. No members of this group are known, although it is possible that some of the heavy sesquiterpenes which apparently do not react with nitrosyl chloride, may belong to this group.

The *tricyclic* group. The members of this group have a comparatively high specific gravity, ranging from 0.930 to 0.939. The cedrene isolated from cedarwood oil by Rousset and the clovane obtained by Wallach from caryophyllene hydrate by treatment with

phosphorus pentoxide, in all probability belong to this group. Patchoulene, obtained by dehydration from patchouly alcohol, is also a member of the tricyclic group.

The *dicyclic* group. This group has a number of representatives and promises to be by far the largest group. The specific gravities of the members of this group fall between the limits 0.898 and 0.918. Cadinene undoubtedly belongs to it, as is shown by its molecular refraction, formation of a dihydrochloride and general chemical behavior. Caryophyllene also belongs to this group, as is definitely shown by recent chemical and optical work. Kanonnikow,³⁶ however, reaches a different conclusion in regard to both of these hydrocarbons which ought to be briefly mentioned here. Kanonnikow applies the true density of bodies to the determination of constitutional differences. According to the dielectric theory of Clausius-Mosotti, when the dielectric constant (according to the electro-magnetic theory of light) is replaced by the square of the index of refraction, n^2 , that part of the entire volume which is occupied by the molecules only, becomes $v = \frac{n^2 - 1}{n^2 + 2}$. From this the true density becomes $D = \frac{d}{v} = \frac{n^2 + 2}{n^2 - 1} d$, where d is the usual density. Kanonnikow has found by calculating the product MD for the hydrocarbons the following empirical formula:

$(MD) = 39.7n + (2n \pm m)H - 4\Pi + a. 9H - b. 6H - b^1. 26H - c. 4H$, in which n is the number of carbon atoms, $2n + m$ the number of hydrogen atoms, a the number of cycles, b the number of ethylene bonds, b^1 the number of naphthalene-ethylene bonds, and c the number of acetylene bonds. H is equal to 0.967. By means of this empirical formula, Kanonnikow finds that cadinene and caryophyllene have three cycles and one ethylene bond, in contradiction to the optical and chemical results obtained with these hydrocarbons.

The molecular refraction of humulene, although slightly high, together with the formation of a liquid hydrochloride which appears to be a di-derivative, place it into this group. The index of refraction of the santalenes had not been determined by Guerbet, but the formation of liquid dihydrochlorides and general chemical behavior, as well as the specific gravity, indicate their relationship with the members of the dicyclic group. The specific gravities and molecular refraction of the uncharacterized sesquiterpenes, araliene, caparapene, galipene, guajene and rhodiene, indicate two double bonds.

³⁶ Journ. russ. phys.-chem. Ges., 31, p. 573; Chem. Centralbl., 1899, II, p. 858.

I. Comparison of the Characterized Sesquiterpenes.

	Cadinene. Wallach ¹	Caryophyllene. Wallach ²	Humulene. Schreiner	Zingiberene. Schreiner	α Guerbet's	β Guerbet's	Santalenes. Chapman & Burgess ⁶	Cedrene (natural). Roussel ⁷
Boiling point.....	274-275°	—	258-260° (20 mm.)	136-137° (20 mm.)	263-266° (14 mm.)	160-161° (32 mm.)	252.5° (0°)	261-262° (10 mm.)
Specific gravity....	.918° (20°)	—	.9085 (15°)	.9030 (20°)	.8977 (20°)	.872 (15°)	.9134 (0°)	.9359 (15°)
Optical rotation....	-98.56°	—	active	-8.46°	inactive	-69°	-73.38°	-28.55°
Index of refract....	1.50647	—	1.50094	1.49976	1.5021	—	1.49399	1.50115
Hydrate.....	—	—	96°	—	not cryst.	—	—	—
Hydrochloride.....	117-118°	117-118°	liquid	69-70°	liquid	168-169°	liquid	—
Hydrobromide.....	124-125°	—	liquid	—	liquid	—	—	—
Nitrosochloride....	—	93-94°	161-163°	157-159°	164-165°	—	96-97°	122°
Nitrosite.....	—	105-110°	148-149°	148-149°	162-163°	—	86-88°	—
" α -compound	—	—	—	113°	120-121°	—	97-98°	—
" β -compound	—	—	—	112-114°	165-168°	—	—	—
Nitropiperidine..	—	—	—	146-148°	—	—	—	—
Nitrobenzyl- amine	—	—	141-143°	—	$\alpha=167^\circ$	136°	—	—
				$\beta=128^\circ$		—	108-109°	{ 101° 104-105°

¹ Ann., 238, p. 82.

² Ann., 271, p. 285; 279, p. 391.

³ Journ. Chem. Soc., 67, p. 64, 780.

⁴ Pharm. Ztg., 45, p. 414.

⁵ Bull. Soc. chim., (3), 23, pp. 218, 544.

⁶ Chem. News, 74, p. 95.

⁷ Bull. Soc. chim., (3), 17, p. 4.

II. Comparison of the More Important Uncharacterized Sesquiterpenes.

	Aralene. Alpers. ¹	Calamene. Kur- batow. ²	Capara- pene. Tapia. ³	Clove. Wallach. ⁴	Galphene (nat.). Beckurts & Troeger. ⁵	Guaiajene. Heine & Co. ⁷	Ledene. Rizza. ⁸	Patchou- lene. Wallach & Tuttle. ⁹	Wintrene. Arata & Canc- nar. ¹⁰	Bisabo- lene. Tu- cholka. ¹¹
Boiling point.....	270°	255-258°	240-260°	261-263°	255-260°	124-128° (18 mm.)	—	264°	254-256°	260-265°
Specific gravity...	.9086 (20°)	.942 (0°)	.9019 (16°)	.930 (18°)	.912 (19°)	.910 (20°)	.920 —	.9349 (0°) —136°*	.939 (25°)	.259- 260.3°
Optical rotation...	-7 to -8°	—	-2.21°	—	—	—	—	—	—	.8914 (17°)
Index of refract...	1.49936	—	1.4953.	1.50066	1.50513	1.50114	—	—	1.50094	1.4608
Hydrochloride....	—	—	—	83° (?)	—	—	—	—	—	79.3°
	From Hemp Oil.	From Carline Thistle. ¹²	From Vignolo. ¹³	From Fendler. ¹⁴	From Semmler. ¹⁵	From Fendler. ¹⁴	From Citronella Oil.	From Pimento Oleifer. ¹⁶	From Valerian Oil. ¹⁷	From Mimosa Laguna Balsam Oil. ¹⁸
Boiling point.....	256-258°	256°	250-253°	255-257°	260-265°	157°	170-172° (16 mm.)	255°	160-165° (50 mm.)	249-251°
Specific gravity...	.9289 (0°)	.807 (15.3°)	.8733 (22.8°)	.911 (20°)	.924 (25°)	.8643 +23.49°	.912 (15°) +1°28'	.925 (15°) —7.23°	.98 (8°) —0.49°	.923
Optical rotation...	-10.81°	—	—	—	—	—	—	—	-9.20°	-9.9°
Index of refract...	—	Solid	liquid	—	—	—	1.51849	—	—	—
Hydrochloride....	—	—	—	—	—	—	—	—	—	114°

¹ Amer. Journ. Pharm., 71, p. 390.

⁷ Products exhibited at Paris 1900.

² Ann., 178, p. 4.

³ Ann., 19, p. 688.

⁴ Ann., 271, p. 284.

⁵ Arch. d. Pharm., 236, p. 408.

⁶ Ann., 279, p. 396.

⁸ Ber., 20, Ref., p. 562.

⁹ Jahrb. d. Pharm., 1889, p. 70.

¹⁰ Arch. d. Pharm., 235, p. 292.

¹¹ Ber., 13, p. 2431; 14, p. 1717.

¹² Ber., 27, Ref., p. 406.

¹³ Chem. Ztg., 13, p. 1158.

¹⁴ Arch. d. Pharm., 288, p. 671.

¹⁵ Ber. S. & Co., Oct. 1899, p. 12.

¹⁶ Ann., 184, p. 1.

¹⁷ Ann., 181, p. 277.

¹⁸ Bull. Soc. chim., 13, p. 924.

¹⁹ Arch. d. Pharm., 221, p. 345.

The *monocyclic* group. The members of this group show a much lower specific gravity than those of the tricyclic and dicyclic groups. Bisabolene and zingiberene probably belong to this group. If bisabolene is a sesquiterpene as its high boiling point would seem to indicate, then it must belong to this group, for its physical constants and formation of a trihydrochloride leave no doubt of the presence of three double bonds. The low specific gravity and molecular refraction of zingiberene speak for three double bonds, but its chemical derivatives so far prepared are not in harmony with this conclusion. The reasons why the optical method is considered the more trustworthy in this case is given under zingiberene.

The sesquiterpene found in the oil of carline thistle by Semmler, if not identical with zingiberene, belongs at least in the same group with it.

The synthetic benzol derivatives of the formula $C_{15}H_{24}$ belong in this class. These are the 1-methyl-4-isopropyl-2-isoamyl benzene prepared by Claus,⁸⁷ and the 4-octyl-1-methyl benzene prepared by Lipinski.⁸⁸ The constitution of these two compounds being known, they can be assigned to the proper nuclear type.

The *chain* group. A possible representative of this group is found in the sesquiterpene isolated by the chemists of Schimmel & Co. from citronella oil. The sesquiterpene has a specific gravity which is even lower than that of zingiberene, and when it is considered that it has been separated from methyl eugenol, having a specific gravity of 1.047, this low specific gravity is significant. The general chemical behavior is in harmony with the view that it is a chain compound. Its molecular refraction, as already mentioned, is rather high.

This brief presentation of the possible members of the various groups, while still rather indefinite, nevertheless shows that among the sesquiterpenes there are compounds possessing widely different properties, which are doubtless due to some such constitutional differences as those suggested above for their classification.

A brief comparison of the more important sesquiterpenes and their derivatives may be given. In the first of the accompanying tables, a comparison of the physical properties of the characterized sesquiterpenes and the melting points of their derivatives is presented, in order to show the analogy as well as the differences between these

⁸⁷ Journ. f. prakt. Chem., (2), 46, p. 489.

⁸⁸ Ber., 31, p. 940.

hydrocarbons. In the second table a comparison of the more important uncharacterized sesquiterpenes, which have received specific names, and also a few of those which are at present only known by the name of the oil from which they are obtained, is likewise presented. These two tables do not comprise all of the sesquiterpenes, but include all those of which anything definite is known. Of those presented it will be noticed that only six are definitely characterized and three others yield solid hydrochlorides of definite melting points. The second table serves to show the almost total absence of characterization by the preparation of chemical derivatives. The fact that many of these have received specific names does not indicate that their individuality is established; some of the unnamed sesquiterpenes are in fact much better known than many of those which have been named by overanxious investigators.

Many of these sesquiterpenes will doubtless be found to be identical with one or the other of the better characterized sesquiterpenes, or with each other.

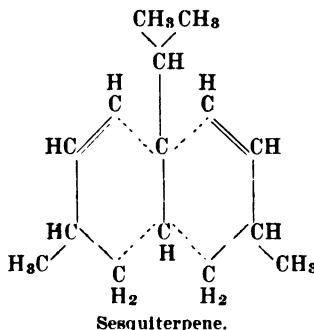
The comparison given in the tables is also useful in pointing out the possibility of such identity. It was such a comparison which suggested the application of the caryophyllene test to the sesquiterpene of pepper oil, with the result that this hydrocarbon has been identified. Such a comparison further indicates, for instance, that araliene and the sesquiterpenes from laurel berry, hemp and valerian oils, may possibly be caryophyllene. Whether this is true or not, can of course only be decided by an actual test, which can now be readily made by applying the nitrosite reaction. The sesquiterpene from carline thistle oil shows some similarity to zingiberene, although the properties given are very meagre. Other comparisons might be made, but these suffice to show that much careful experimental work remains to be done before the sesquiterpenes can be considered sufficiently characterized for their detection and identification.

In connection with this classification based on constitutional differences, it will not be amiss to consider briefly the possibility of ascertaining the constitution of these hydrocarbons, both by "Abbau" and by synthesis. Several attempts have been made to synthesize sesquiterpenes. In 1867 Reboul³⁹ succeeded in polymerizing valerenone with conc. sulphuric acid, obtaining as one of the products a hydrocarbon C₁₅H₂₄, trivaleriene (see this under synthetic sesquiterpenes). A similar result was obtained by Bouchardat⁴⁰ in 1878.

³⁹ Compt. rend., 64, p. 419; Ann., 148, p. 873.

⁴⁰ Compt. rend., 87, p. 654; Bull. Soc. chim., 38, p. 24.

Wallach⁴¹ in 1887 attempted to prepare cadinene dihydrochloride from the polymerization products of pinene, but failed. Thinking that cadinene might be produced by polymerizing a pentene rather than a terpene, he tried various methods of polymerization on isoprene, C₅H₈. Although he obtained a hydrocarbon boiling between 260—280°, he was unable to prepare a solid dihydrochloride from the compound. In a later article Wallach⁴² suggests several formulas for terpenes and one for a sesquiterpene. These formulas are based on the supposition that these hydrocarbons are, in part at least, polymerization products of a pentene. The sesquiterpene he considers as resulting from the polymerization of three molecules of isoprene as shown by the following formula:



Of this formula Wallach remarks: "Bei einem derartigen Aufbau würden den Sesquiterpenen und (wie man leicht findet) auch den Polymeren je zwei doppelte Kohlenstoffverbindungen zukommen, was den bisher bekannten Thatsachen entspricht." After the exposition of the possibilities of isomeric hydrocarbons C₁₅H₂₄ in the preceding chapter it is well-nigh needless to call attention to the fact that the above statement is altogether too narrow a view, and is not even supported by the facts now recorded of well characterized sesquiterpenes.

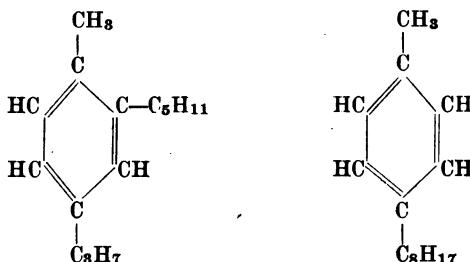
The syntheses of the benzene derivatives of the formula C₁₅H₂₄ by Claus⁴³ and by Lipinski⁴⁴ are of interest as they furnish us with sesquiterpenes of known constitution, but they do not agree with any of the natural sesquiterpenes, which probably have some cycle or cycles other than that of benzene in their nuclear structure.

⁴¹ Ann., 288, p. 88.

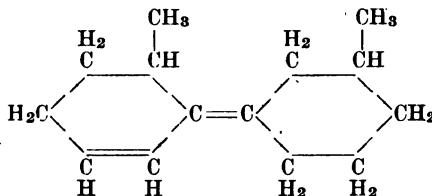
⁴² Ann., 239, p. 49.

⁴³ Journ. f. prakt. Chem., (2), 46, p. 489.

⁴⁴ Ber., 31, p. 940.



Another line of synthesis for sesquiterpenes is suggested by recent work with cyclo methyl hexanone. Thus Dorrance⁴⁵ was able to get from two molecules of cyclo methyl hexanone, $C_7H_{12}O$, by a series of reactions the hydrocarbon $C_{14}H_{22}$, to which he assigns the formula:



By using one molecule of cyclo methyl hexanone and one molecule of a cyclo ethyl hexanone or cyclo dimethyl hexanone, it ought to be possible to obtain a hydrocarbon $C_{15}H_{24}$, namely, a sesquiterpene.

While such syntheses would furnish us with sesquiterpenes of known constitution it is questionable whether they would agree with any of the known natural sesquiterpenes. The problem of the constitution of these compounds is a difficult one. It will probably have to be solved by methods of oxidation and hydrolysis, that is, a breaking down of the complex structures into simpler compounds, the constitution of which may be known or more readily determined. The oxidation of the sesquiterpenes has been but little studied, and that little offers no clue as to the nuclear structure of any of them. If zingiberene is monocyclic, it ought to be much simpler to work on it than the members of the dicyclic group. Direct oxidation with permanganate or bichromate yield very unsatisfactory results, but anhydrous copper sulphate seems to be more favorable in its action. Some preliminary experiments show that zingiberene is very readily oxidized by this oxidizing agent, with the formation of an oily body, the nature of which has not been determined.

⁴⁵ Dissert., Göttingen, 1897.

IV. The Occurrence of Sesquiterpenes in the Vegetable Kingdom.

The sesquiterpenes are usually found in volatile oils as such, or in the form of sesquiterpene hydrates,⁴⁶ alcohols belonging to the so-called camphor group. These hydrates, by dehydration, give rise to sesquiterpenes which are rarely identical with a natural sesquiterpene, being more often distinctive compounds. Many oils, such as cedar-wood, santalwood, copaiba balsam, gurjun balsam, ginger, cubeb, etc., consist principally of a sesquiterpene or a sesquiterpene hydrate. The latter compound is found more often in oils distilled from old drug, and thus appears to be produced from the sesquiterpene during the ageing process, although the exact conditions for this change are not known. In other oils, the sesquiterpene is present in almost insignificant quantities only.

The occurrence of the sesquiterpenes in the vegetable kingdom is given in a tabulated form in the following pages. The arrangement is that of Engler's syllabus of plant classification. Such a tabulation shows that the sesquiterpenes are very widely distributed as products of plant life. The list includes thirty families, comprising fifty-six genera and upward of sixty-nine known species. The number of volatile oils in which sesquiterpenes have been found is upward of seventy-four, some of these being obtained from unknown botanical sources.

The lack of characterization of the sesquiterpenes makes it impossible to draw any general conclusions, but a few interesting facts are nevertheless brought out by such a tabulation. In the pine family, for instance, it will be seen that the sesquiterpene cadinene is restricted to the needles. Again, two distinct sesquiterpenes may occur in different parts of the same plant as in the case of *Juniperus virginiana*, where cadinene occurs in the leaves, and cedrene in the wood. It is also interesting to note that closely allied species may contain different sesquiterpenes, thus for instance, *Piper nigrum* contains caryophyllene, and *Piper betle* and *Piper cubeba* contain cadinene.

⁴⁶ Under the term sesquiterpene hydrates only alcohols of the formula $C_{15}H_{26}OH$ are to be understood. There seems to be a tendency to designate all high boiling alcohols obtained from volatile oils as sesquiterpene hydrates. This is especially true of the alcohols $C_{15}H_{26}OH$, which are evidently not sesquiterpene hydrates at all, but the hydrates of a hydrocarbon $C_{15}H_{22}$ belonging to a series of hydrocarbons less saturated than the sesquiterpenes.

Such an arrangement into families may often indicate relationships between the sesquiterpenes as well. Thus, for instance, the sesquiterpenes found in the pine family are all, with the exception of the cedrene from the wood of *Juniperus virginiana*, cadinene. The close relationship between *Acorus calamus* and *Acorus spurius* makes it probable that the same sesquiterpene is contained in both. A similar relationship might exist in the case of the *Copaifera* species, *Dipterocarpus* species, and others, although no general conclusion of this nature can be drawn. A botanical relationship of this kind can merely indicate a possible chemical relationship of the sesquiterpenes contained in the plant, but this must in all cases be substantiated by a careful comparison of physical constants, and when possible, by the preparation of characteristic derivatives.

SPECIAL PART.

1. Araliene.

In 1899 Alpers⁴⁷ reported on an examination of the volatile oil obtained by steam distillation from the rhizome of *Aralia nudicaulis* or wild sarsaparilla. The greater portion of the oil boiled between 185—195° (80 mm.) or 260—270° (at. p.). Oxygen was present, and the oil was, therefore, treated with metallic sodium. About two thirds of the oil thus treated distilled at 189° (80 mm.) or at 270° (at. p.). Elementary analysis and vapor density determination showed it to be a sesquiterpene. From the liquid hydrochloride, by treatment with sodium acetate, a sesquiterpene was regenerated. No solid bromide or nitrosochloride was obtained. Chloroform and sulphuric acid produce a purple-red color, acetic acid and sulphuric acid a wine-red color.

Alpers concludes that this is a new sesquiterpene and proposes the name of araliene, basing his assumption on the physical properties of a very small and necessarily impure sample, and on his totally negative chemical results; whereas, a comparison of the physical constants of araliene with those of pure caryophyllene renders it not improbable that the araliene of Alpers is impure caryophyllene.

⁴⁷ Amer. Journ. Pharm., 71, p. 370.

The Occurrence of Sesquiterpenes in the Vegetable Kingdom.

	Sesquiterpene Hydrates.	Uncharacterized Sesquiterpenes.	Sesquiterpene Hydrates.
<i>Pinaceae.</i>			
<i>Pinus sylvestris</i> (needles)	—		
“ <i>montana</i> (“)	—		
<i>Picea excelsa</i> (“)	—		
<i>Tsuga canadensis</i> (needles)	?		
<i>Abies alba</i> (needles)	—		
“ <i>oxycedrus</i> (berries)	—		
“ <i>sabina</i>(destruct. dist.)	—		
“ <i>virginiana</i> (leaves)	—		
“ “ (wood)	—		
		Cedrene.	
<i>Gramineae.</i>			
<i>Andropogon nardus</i> <i>muriaticus</i>	—		
<i>Araceae.</i>			
<i>Acorus calamus</i>	Calamene.		
“ <i>spurious</i>	—		
<i>Liliaceae.</i>			
<i>Allium sativum</i>	?		
<i>Zingiberaceae.</i>			
<i>Kaempferia galanga</i>	—		
<i>Zingiber officinale</i>	—		
<i>Piperaceae.</i>			
<i>Piper nigrum</i> <i>cubeba</i>	—		
“ <i>betel</i>	—		
		Cuben camphor.	

		Uncharacterized Sesquiterpenes.	Sesquiterpene Hydrates.
<i>Salicaceae.</i>			
<i>Populus nigra.</i>			
<i>Moraceae.</i>			
<i>Humulus lupulus</i>			
<i>Cannabis sativa.</i>			
" <i>gigantea.</i>			
<i>Santalaceae.</i>			
<i>Santalum album.</i>			
<i>Magnoliaceae.</i>			
<i>Drimys winteri</i>			
<i>Anonaceae.</i>			
<i>Cananga odorata.</i>			
<i>Monimiaceae.</i>			
<i>Unknown species</i>			
<i>Lauraceae.</i>			
<i>Cinnamomum camphora</i>			
<i>Nectandra caparapi</i>			
<i>Sassafras officinale</i>			
<i>Laurus nobilis</i> (berries)	?		
<i>Rosaceae.</i>			
<i>Spiraea ulmaria</i>			
<i>Leguminosae.</i>			
<i>Copaiifera officinalis</i> and other species			
" species (unknown)			
<i>Zygophyllaceae.</i>			
<i>Bulnesia sarmienti</i>			Guajol.

	Uncharacterized Sesquiterpenes.	Sesquiterpene Hydrates.	
<i>Rutaceae.</i>			
<i>Cusparia trifoliata</i>			
<i>Citrus limonum</i>	Zingiberene.	Galipol.	
<i>Citrus bigaradia</i>		Amyrol.	
<i>Amyris balsamifera</i>			
<i>Burseraceae.</i>			
<i>Commiphora species</i>		Bisabolene.	
<i>Boswellia carterii</i>		Conimene.	
<i>Icica heptaphylla</i>		—	
<i>Bursera aloxyylon</i>		—	
<i>Meliaceae.</i>			
<i>Cedrela odorata</i> and other species.....		Gurjunene.	
<i>Euphorbiaceae.</i>		—	
<i>Croton eluteria</i>		—	
<i>Dipterocarpaceae.</i>			
<i>Dryobalanops camphora</i>			
<i>Dipterocarpus species</i>			
<i>Dipterocarpus turbinatus</i> and other species.....			
<i>Canellaceae.</i>			
<i>Canella alba</i>		—	
<i>Myrtaceae.</i>			
<i>Pimenta officinalis</i>			
<i>Eugenia caryophyllata</i> (buds), “			
<i>(stems)</i>			
<i>Araliaceae.</i>			
<i>Aralia nudicaulis</i>		Araliene.	

<i>Umbelliferae.</i>	<i>Uncharacterized Sesquiterpenes.</i>	<i>Sesquiterpene Hydrates.</i>
<i>Apium graveolens</i>	—	—
<i>Archangelica officinalis</i>	—	—
<i>Ferula assa foetida</i> and <i>other species</i>	—	—
“ <i>rubicundus</i> ”	—	—
<i>Ericaceae.</i>		
<i>Ledum palustre</i>	—	—
<i>Convolvulus scoparius</i> and <i>C. floridus</i>	—	—
<i>Labiatae.</i>		
<i>Lavandula vera</i>	—	—
“ <i>spira</i> ”	—	—
<i>Salvia officinalis</i>	—	—
<i>Thymus serpyllum</i>	—	?
<i>Mentha piperita</i>	—	?
“ <i>arvensis</i> var. <i>niperascens</i>	—	?
<i>Pogostemon patchouly</i>	—	—
<i>Ocimum basilicum</i>	—	—
<i>Valerianaceae.</i>		
<i>Valeriana officinalis</i>	—	—
“ “ <i>var. angustifolia</i>	—	—
<i>Zingiberaceae.</i>		
<i>Ageratum conyzoides</i>	—	—
<i>Solidago canadensis</i>	—	—
<i>Ariemesia absinthium</i>	—	—
<i>Erechtites hieracifolia</i>	—	—
<i>Carlinea acutalis</i>	—	—
<i>Actaea spicata</i>	—	—
<i>Attractylis ovata</i>	—	—
<i>Attractylol.</i>		

	B. p.	Sp. gr.	n_D	$[\alpha]_D$
Caryophyllene..... (Schreiner and Kremers)	136-137° (20 mm.)	0.9030 (20°)	1.49976	-8.96
Araliene.....	270°	0.9086 (20°)	1.49936	-7 to -8
Caryophyllene..... (Wallach)	258-260°	0.9085 (15°)	1.50094	active.

2. Atractylene.

By dehydrating atracylol with acid potassium sulphate, Gadamer and Amenomiya,⁴⁸ obtained a sesquiterpene, to which they applied the name atracylene. They also obtained a second hydrocarbon from an oily chlorhydrate, prepared by acting on atracylol in ether solution with hydrochloric acid gas. This they also designated atracylene, although the two hydrocarbons had quite different properties. Based on the molecular refractions, the authors conclude that the two hydrocarbons differ from one another by a double bond. However, as neither of the sesquiterpenes was obtained in a pure state, the physical constants can hardly be relied upon to decide this point. No chemical derivatives were obtained. Attempts to prepare the hydriodide, bromide, and hydrate failed. Although the authors give the misleading title of "atracylene nitrosochloride" to a section of their experimental work, they only obtained a greenish oil which readily decomposed.

Physical properties. Atractylene by dehydration with KHSO_4 :
B. p. 260-261° (760 mm.); $d_{15}^{20} = 0.9154$; $d_{15}^{20} 0.9101$ $n_D = 1.50893$.

Atractylene from the oily chlorhydrate prepared from atracylol:

B. p. 133-141° (14.5 mm.); $d \frac{20}{4} = 0.9267$ $n_D = 1.50565$.

Sesquiterpene hydrate yielding atracylene. Atracylol.

This sesquiterpene hydrate was obtained from the oil of *Atractylis ovata* Thunb., which becomes crystalline shortly after being distilled. Neno⁴⁹ assigned to it the formula $C_{10}H_{18}O$, but Gadamer and Amenomiya give it the formula $C_{15}H_{26}O$. It appears to react with phenylisocyanate, hydrochloric and hydrobromic acids, iodine, nitric acid, acetic acid and its anhydride, also with benzoyl chloride, but no characteristic compounds could be isolated, nor are the esterification results in any case quantitative. Atracylol readily splits

⁴⁸ Arch. d. Pharm. 241, p. 88.

⁴⁹ Journ. Pharm. Soc. of Japan, No. 129, p. 1074.

off water. On these results the authors base the opinion that atractylol is a tertiary alcohol.

Properties. Loose, soft needles of peculiar odor and possessing a bitter, somewhat scratching taste.

M. p. 59°; B. p. 290—292 (760 mm.); 162° (15 mm.); n_D (in overcooled condition)=1.51029 to 1.51101. Optically inactive.

3. Bisabolene.

In 1897 Tucholka⁵⁰ obtained from the oil of bisabol myrrh a hydrochloride from which he prepared a hydrocarbon, bisabolene, boiling at 259—260.3°. Analysis and molecular weight leave Tucholka in doubt whether the hydrocarbon is a terpene, $C_{10}H_{16}$, or a diterpene, $C_{20}H_{32}$. To the hydrochloride, however, he assigns the formula $C_{20}H_{32}.4HCl$. On account of the high boiling point, however, Charabot, Dupont and Pillet⁵¹, class bisabolene with the sesquiterpenes, to which it doubtless belongs. Its specific gravity is high for a terpene, but rather low for a sesquiterpene, and this, taken together with the refraction, indicates a sesquiterpene with three double bonds. It would, therefore, fall into the same class with zingiberene. The dispersion of the two compounds is also very close, being 0.01186 and 0.01278 respectively, for $n_F - n_C$. The formation of a trihydrochloride, $C_{15}H_{24}3HCl$ (or $C_{20}H_{32}4HCl$, according to Tucholka) is in harmony with this view. Whether the hydrocarbon naturally present in the oil is identical with bisabolene generated from the hydrochloride is not apparent.

Preparation. The trihydrochloride, prepared from the oil as described below, is heated with anhydrous sodium acetate and glacial acetic acid.⁵² The hydrocarbon is separated by steam distillation, washed with alkali, again distilled with steam and dried with solid potassa.

Physical properties. The colorless bisabolene has the following properties:

B. p. 259—260.3°; $d_{17}^{\circ} = 0.8914$; $n_D = 1.4608$; ⁵³ $n_F - n_C = 0.01186$.

Chemical properties. No chemical properties of the regenerated bisabolene are given.

The trihydrochloride, $C_{15}H_{24}3HCl$, was prepared from the crude

⁵⁰ Arch. d. Pharm. 235, p. 292.

⁵¹ Les Huiles Essentielles, p. 894.

⁵² See Ann., 239, p. 24.

⁵³ Comp. p. —.

oil. Hydrogen chloride was passed into the cooled solution of one part of oil in six volumes of anhydrous ether until crystals separated. The ether was then distilled off to about $\frac{1}{6}$ its original volume and the oily residue kept in a freezing mixture at -21° for two days. At the end of this time the reddish brown liquid had changed to a mass of crystals, which were collected and washed with cold alcohol. The crystals were purified by several crystallizations, first from alcohol and then from ether. When slowly crystallized, the trihydrochloride separated in well developed, tabular crystals of hexagonal habit, but which belong to the rhombic system, as shown by their optical behavior. M. p. 79.3° ; $[\alpha]_D = 35^{\circ} 17'$ in chloroform and $37^{\circ} 16'$ in ether solution.

4. Cadinene.

Synonyms.

The class names in the older nomenclatures, such as,

- Aetherisches Cubebenöl,
- Paracamphe,
- Cedrene,
- Sesquiterebene,
- Sesquiterebenthene,
- Sesquiterpene,

and the specific names,

- Cubebene,
- Galipene,
- Amyrene,
- Cadinene.

Cadinene, before it was characterized, is often referred to in the early literature under the general class name of paracamphe, sesquiterpene, etc., and also by the name of the oil in which it occurs, for instance, "ätherisches Cubebenöl."⁵⁴ The class name of sesquiterpene is still applied to it even after Wallach had suggested the name of cadinene. Thus Wallach and Conrady⁵⁵, in giving the physical constants of cadinene and its derivatives, continually refer to it as "Sesquiterpen" and to its derivatives as "Sesquiterpen dihydrochlorid" etc. Bornemann in "Die Flüchtigen Oele," published in 1891,

⁵⁴ Schmidt, Arch. d. Pharm., 191, p. 22.
⁵⁵ Ann., 252, p. 150.

does not mention the word cadinene, but always calls it "Sesquiterpen" and thus fails to differentiate between different sesquiterpenes, largely, no doubt, because at the time at which he wrote exceedingly little was known about the characteristics of any of the other sesquiterpenes. This, no doubt, also explains why other writers sometimes use the word cadinene as though it were synonymous with sesquiterpene.

The word cubebene was formerly largely applied to this hydrocarbon, because it was first found in oil of cubeb. It is now almost universally replaced by the word cadinene. The designation cubebene is now restricted to the sesquiterpene from cubeb camphor.

Galipene may also be mentioned as a synonym for cadinene. This was at first supposed to be a distinct sesquiterpene by Beckurts and Troeger⁵⁶ (1897), but its derivatives have been shown to be true cadinene derivatives. The name is derived from *Galipea cusparia* St. Hil. (*Cusparia trifoliata* Engl.), the plant yielding angostura bark oil, in which the sesquiterpene was found. The designation galipene is now applied to another sesquiterpene found in the same oil.

Amyrene, as the dextrogyrate sesquiterpene of West Indian sandal-wood oil from *Amyris balsamifera* is called by Heine & Co.,⁵⁷ was shown by Deussen⁵⁸ to yield cadinene derivatives, and may, therefore, be included in the list of synonyms for cadinene.

The name cadinene was proposed by Wallach⁵⁹ in 1887, because the dihydrochloride of the sesquiterpene was obtained in large quantities from oil of cade.

History and General Discussion.

The history of cadinene is closely connected with the chemical study of cubeb oil. As early as 1840, Soubeiran and Capitaine⁶⁰ found this oil to consist largely of a sesquiterpene which yielded with hydrochloric acid gas a crystalline hydrochloride melting at 181° and being laevo-rotatory. In 1860 Lallemand⁶¹ obtained a similar hydrochloride melting at 125° from a sesquiterpene occurring in the oil from *Dryobalanops camphora*. Lallemand regenerated the sesquiterpene from this hydrochloride by treatment with lead oxide or

⁵⁶ Arch. d. Pharm., 285, pp. 518, 684; 286, p. 892.

⁵⁷ List of products exhibited at Paris, 1900.

⁵⁸ Arch. d. Pharm., 288, p. 149.

⁵⁹ Ann., 288, p. 78.

⁶⁰ Journ. d. Pharm., 26, p. 76; Ann., 34, p. 828.

⁶¹ Ann. d. Phys., (3) 57, p. 401; Ann., 114, p. 198.

mercuric oxide at 100°, or saponification with alcoholic potassium. This regenerated hydrocarbon boiled at 260°, was strongly laevo-rotatory and combined again with hydrochloric acid to yield the same hydrochloride.

Schmidt⁶² in 1870 and 1877 and Oglialoro⁶³ in 1875, obtained a hydrochloride from cubeb oil, melting at 118°. Oglialoro regenerated the hydrocarbon by heating this hydrochloride with water to a high temperature. The hydrocarbon boiled at 264—265° when rectified and could be changed back into the original hydrochloride by hydrochloric acid gas.

Wallach⁶⁴ in 1887 undertook a more detailed study of this sesquiterpene. He found that the corresponding fractions of cubeb, patchouly, galbanum, savine, and cade oil, all yielded the same dihydrochloride, melting at 117—118°. As cade oil contained the sesquiterpene in large quantities, Wallach proposed for it the name of cadinene. By heating this dihydrochloride with aniline, or with anhydrous sodium acetate in glacial acetic acid solution, the hydrocarbon was regenerated. This regenerated hydrocarbon again yielded the same dihydrochloride. He also prepared the dihydrobromide, melting at 124—125°, and the dihydroiodide, melting at 105—106°.

Since that time the dihydrochloride of cadinene has been obtained from the high boiling fractions of many oils. These will be considered specifically under the heading of occurrence. In all these cases, however, the formation and melting point, and rarely also other properties, of the dihydrochloride have been the only evidence of the identity of the hydrocarbons in these oils. In many articles, the word cadinene is even used as synonymous with any high boiling fraction, possessing the general properties of a sesquiterpene, without chemical identification. It is not at all certain that cadinene really exists in all of these oils. Cadinene is reported⁶⁵ to exist in asafoetida oil, but Semmler⁶⁶ has shown in his work that the hydrocarbon is not present in the oil as such, but is generated from an oxygenated product by repeated treatment with sodium. It is likewise reported⁶⁷ to be present in pepper oil, but the sesquiterpene from this oil has

⁶² Arch. d. Pharm., 191, p. 21; Ber., 10, p. 190.

⁶³ Gazz. chim., 5, p. 567; Ber. 8, p. 1857.

⁶⁴ Ann., 288, p. 78.

⁶⁵ Ann., 271, p. 297; Charabot, *Les Huiles Essentielles*, p. 894; Heusler, *Die Terpene*, p. 148.

⁶⁶ Arch. d. Pharm., 229, p. 17.

⁶⁷ Ber. v. S. & Co. Oct. 1898, Suppl. p. 88; Charabot, *Les Huiles Essentielles*, p. 894; Heusler, *Die Terpene*, p. 148.

been shown to be caryophyllene and not cadinene by Schreiner and Kremers.⁶⁸ Several other cases of this nature might be mentioned, where the only fact to warrant the assumption that cadinene is present, is the color reaction suggested by Wallach.⁶⁹ A color reaction of this kind is at best only a mere indication of the possible presence of cadinene, but is by no means conclusive.

Attention should here be called to the tendency of the terpenes proper to change from one into the other through the action of hydrochloric acid and it is not improbable that similar inversions may take place with the sesquiterpenes. As dipentene dihydrochloride results under certain conditions not only from pinene but also from limonene and several socalled terpene hydrates, so may the sesquiterpene dihydrochloride melting at 118°, and called cadinene dihydrochloride, result from several distinct sesquiterpenes and their hydrates. Although cadinene when regenerated from the dihydrochloride, is always strongly laevogyrate, the original fractions from which the hydrochloride was obtained show a great diversity of optical activity, many being strongly dextrorotatory.

Beckurts and Troeger⁷⁰ in 1897 contributed some interesting observations which seem to point unmistakably toward inversion in the group of the sesquiterpenes. They succeeded in getting from fraction 260—270° of angostura oil an oxygenated product, C₁₅H₂₆O. This compound is optically inactive, readily splits off water when heated and is very difficult to obtain. For this compound they propose the name of galipol. From galipol and also from fraction 250—280°, they obtained by heating with acetic acid anhydride in a sealed tube, a sesquiterpene, which showed a rotation of + 18° in a 100 mm. tube. From this hydrocarbon, which they called "gali-pene," they prepared a dihydrochloride melting at 114—115°, and a dihydropbromide melting at 123°. The original oil was strongly laevogyrate, viz. — 50°; the alcohol was inactive, and the hydrocarbon generated from the alcohol, also that obtained from fraction 250—280° with acetic acid anhydride, was dextrogyrate, viz. + 18°. From this it appears that an inversion of the sesquiterpene in the original oil has taken place. In a later article⁷¹ they show that by the use of different dehydrating agents, entirely different results are

⁶⁸ Pharm. Archives, 4, p. 61; Proc. Amer. Pharm. Assoc., 49, p. 849.

⁶⁹ Ann., 288, p. 87.

⁷⁰ Arch. d. Pharm., 285, p. 518.

⁷¹ Arch. d. Pharm., 285, p. 684.

obtained from the same oil. The original oil was again strongly laevogyrate; by treatment with acetic acid anhydride the optical activity was changed to +20°; by treatment with phosphorus pentoxide it was changed to -10°. Further, they were able to isolate an *inactive* sesquiterpene from the oil by fractional distillation and treatment with phosphorus pentoxide. In a third contribution⁷² they report that the dihydrochloride and dihydrobromide formerly reported as "galipene" compounds are identical with the corresponding cadinene derivatives, although they result from a dextrogyrate hydrocarbon, whereas the known cadinene is strongly laevorotatory. This time they suggest the name of galipene for the inactive sesquiterpene instead of the dextrogyrate variety mentioned above. These observations leave the identity of the sesquiterpenes in angostura oil in a very unsatisfactory condition.

Other cases of disagreement in physical properties similar to the above are on record. H. v. Soden⁷³ found a dextrogyrate sesquiterpene in West Indian sandal-wood oil, which is designated by Heine & Co.⁷⁴ as "amylene." Deussen,⁷⁵ however, was able to get derivatives of the laevogyrate cadinene from this dextrogyrate hydrocarbon. Grimal* on the other hand, obtained dextrogyrate cadinene derivatives, agreeing in properties with the usual laevogyrate forms, from a dextrogyrate fraction of atlas cedar oil. Schimmel & Co.⁷⁶ found that both the dextrogyrate Cuban cedrela wood oil and the laevogyrate Costa Rica variety, yielded large amounts of cadinene dihydrochloride. Reyhler⁷⁷ found that the rotation of the sesquiterpene in ylang-ylang and cananga oils yielding cadinene dihydrochloride was greatly affected by the heat of distillation under ordinary pressure, the action going so far as to produce an inversion in the rotation. This change did not take place when the distillation was carried on under diminished pressure. All these results clearly show that inversion may take place and that at least two different physical modifications of the same sesquiterpene yield the same dihydrochloride. Identification based only on such a compound may, therefore, lead to wrong conclusions.

In view of these facts it appeared highly essential that other

⁷² Arch. d. Pharm., 286, p. 897.

⁷³ Pharm. Ztg., 45, pp. 229, 878.

⁷⁴ List of products exhibited at Paris 1900.

⁷⁵ Arch. d. Pharm., 288, p. 149.

* Comp. rend., 185, pp. 582, 1059.

⁷⁶ Ber. v. S. & Co., April 1892, p. 41.

⁷⁷ Bull. Soc. chim., (8) 11, pp. 576, 1045.

derivatives of these sesquiterpenes be made before considering them identical. The success with the nitroso compounds of caryophyllene led Schreiner and Kremers⁷⁸ to attempt the preparation of similar compounds of cadinene. These attempts proved fruitless at first, but the conditions for the formation and separation of some nitroso derivatives were finally found. So far the nitrosate and nitroso-chloride have been prepared; the nitrosite has not yet been separated as its solutions appear to decompose very readily. It is, however, a noteworthy fact that while these two derivatives can now be made with comparative ease from the pure regenerated hydrocarbon, they have so far not been prepared from the original fraction, which yielded the dihydrochloride in large quantity. Whether this is due to the presence of impurities in the fraction or to a difference in the sesquiterpene itself, cannot be stated.

From the foregoing it will be seen that while cadinene is reported as widely distributed, these statements must be taken with reserve. Cadinene is, moreover, reported in text books and special treatises on volatile oils and their constituents as the only well characterized and best known of the sesquiterpenes. Such indeed was the case at the time of publication of these treatises. The reverse is, nevertheless, true at present. Of the characterized sesquiterpenes, cadinene really comes last and until further evidence is forthcoming the word cadinene ought to be applied only to the sesquiterpene, which has been regenerated from the dihydrochloride and not to the fractions of volatile oils which yield this dihydrochloride. The regenerated hydrocarbon is well characterized and deserves a place in chemical literature as a chemical unit, but the compounds yielding the dihydrochloride may or may not be cadinene and further study along this line is necessary before this point can be cleared up.

Occurrence.

Under this heading the oils in which cadinene has been reported as a constituent will be discussed. The subject matter has been arranged according to the position of the plants, from which the oils are obtained, in Engler's Syllabus. The list of plants yielding these oils has already been given in the chapter on the occurrence of the sesquiterpenes in general. Of those yielding cadinene, the list com-

⁷⁸ Pharm. Archives, I. c.

prises twelve families, including twenty-one genera yielding twenty-seven distinct oils.

The presence of cadinene in these oils has in nearly all cases been determined by the formation of the dihydrochloride melting at 117–118°. The doubtful oils, in which cadinene has been erroneously stated to be present, or where it is at best only indicated by means of color reactions, have, for the sake of completeness, also received mention in this compilation.

PINACEAE.

Pinus silvestris. Pine Needle Oil.

According to Bertram and Walbaum⁷⁹ the highest boiling fractions of the saponified oil of the needles from *Pinus silvestris*, gave with hydrochloric acid gas a dihydrochloride melting at 118°, identical with cadinene dihydrochloride.

Pinus montana. Pine Needle Oil.

Bertram and Walbaum⁸⁰ found that the optically inactive fractions of pine needle oil from *Pinus montana* boiling above 250° yielded cadinene dihydrochloride melting at 118°.

Picea excelsa. Pine Needle Oil.

According to Bertram and Walbaum⁸¹ the fraction of pine needle oil from *Picea excelsa*, boiling above 260°, had a rotation of $\alpha_D = -6^\circ 40'$, and yielded cadinene dihydrochloride melting at 118°.

Tsuga canadensis. Hemlock Needle Oil.

Cadinene is mentioned by Schimmel & Co.,⁸² and also by Heusler⁸³ as a constituent of hemlock oil, without, however, giving any proof or reference. Bertram and Walbaum⁸⁴ in 1893 report the presence of a sesquiterpene, but did not identify it. Gildemeister and Hoffmann⁸⁵ in 1899 still give the sesquiterpene as undetermined.

Abies alba. Pine Needle Oil.

According to Bertram and Walbaum⁸⁶ the saponified pine needle oil from *Abies alba* contains sesquiterpene ("Wallach's Cadinene").⁸⁷ No properties are given.

⁷⁹ Arch. d. Pharm., 231, p. 900.

⁸⁰ Arch. d. Pharm., 231, p. 297.

⁸¹ Arch. d. Pharm., 231, p. 296.

⁸² Ber. v. S. & Co., Oct. 1893, Suppl., p. 21.

⁸³ Die Terpene, p. 168.

⁸⁴ Arch. d. Pharm., 231, p. 295.

⁸⁵ Die Aeth. Oele, p. 340.

⁸⁶ Arch. d. Pharm., 231, p. 291.

⁸⁷ Ber. v. S. & Co., April 1893, p. 29.

Cedrus atlantica, Algerian variety of *Cedrus libani*. Oil of Atlas Cedar.

Grimal* examined oil of atlas cedar and found the light boiling fractions to contain cadinene, which he identified by preparing the dichlorhydrate, m. p. 117–118°, and also the dibromhydrate, m. p. 124–125°. Sesquiterpene alcohols were also present but not identified. In a second article Grimal** shows the sesquiterpene to be d-cadinene and prepares d-cadinene derivatives, from which he again regenerates d-cadinene. The sesquiterpene isolated by distillation from the oil had the following properties: $d_{15} = 0.9224$; $n_D = 1.5107$; $[\alpha]_D = +48^{\circ}7'$; b. p. = 273–275°.

Juniperus communis. Oil of Juniper Berries.

According to Schimmel & Co.⁸⁸ the high boiling fraction gives cadinene dihydrochloride, melting at 118°.

Juniperus oxycedrus. Cade Oil.

Cade oil is obtained by the destructive distillation of the wood. In 1887 Wallach⁸⁹ obtained from fraction 260–280° of cade oil the same dihydrochloride as from the corresponding fraction of cubeb oil. As the oil yielded large amounts of this sesquiterpene, he proposed the name of cadinene for the hydrocarbon. The dihydrochloride obtained from this oil was the starting point of Wallach's researches on cadinene.

Troeger and Feldmann⁹⁰ in 1898 attempted to prepare the dihydrochloride from cade oil in order to compare the regenerated sesquiterpene with the cadinene found in angostura oil. The fraction 260–280° yielded, however, only very little of the dihydrochloride or dihydrobromide, showing that only a small amount of cadinene could be present. Repeated distillation showed the oil to consist mainly of an inactive sesquiterpene.

These results agree with observations made in this laboratory.⁹¹ One sample of oil gave excellent yields of dihydrochloride, another only a very small amount, and a third gave none at all. In all these cases the fraction 260–280° was used. These fractions were slightly dextrogyrate in the last two cases. The rotatory power of the fraction from the first oil had not been determined.

* Compt. rend., 185, p. 582.

** Compt. rend., 185, p. 1057.

⁸⁸ Ber. v. S. & Co., April 1890, p. 43.

⁸⁹ Ann., 288, p. 82.

⁹⁰ Arch. d. Pharm., 286, p. 692.

⁹¹ Not published,

Reychler⁹² noticed that the cadinene from ylang-ylang and cananga oils suffered a great change in rotation on being distilled under ordinary pressure. In one case an inversion to a dextrogyrate sesquiterpene took place. Whether this dextrogyrate sesquiterpene still forms a hydrochloride, Reychler did not determine. It is highly probable that the results noticed by Troeger and Feldmann and also in this laboratory are due to a similar cause. On the other hand it is not improbable that the sesquiterpene of cade oil is not always cadinene, and that another sesquiterpene may often be present. Cade oils of greatly varying properties are to be found in commerce, and the oil is not always distilled from the wood of *Juniperus oxycedrus* only, but often from mixtures of these with other woods.⁹³

Cathelineau and Hausser⁹⁴ avoid the application of direct heat to the oil, but distill the nonphenol portion of the oil with water vapor, and then mix it, without further fractionation, with alcohol and treat it with hydrochloric acid gas.⁹⁵ In this way they obtained a very satisfactory yield of dihydrochloride from the oil.

Juniperus sabina. Oil of Savin.

Wallach⁹⁶ mentions oil of savin in the list of oils from which he obtained cadinene dihydrochloride. Umney⁹⁷ mentions the presence of polyterpenes (?) boiling at 226°.

Juniperus virginiana. Oil of Cedar Leaves.

According to Schimmel & Co.⁹⁸ the high boiling portions of oil of cedar leaves contained cadinene as was shown by the preparation of its dihydrochloride.

PIPERACEAE.

Piper nigrum. Black Pepper Oil.

Eberhardt⁹⁹ in 1887 reported the presence of a sesquiterpene in black pepper oil. In 1893 Schimmel & Co.¹⁰⁰ mention cadinene as a constituent of this oil, without, however, giving proof or reference. The same is done by Heusler.¹ Schreiner and Kremers,² however, showed this sesquiterpene to be caryophyllene (see this). It is possible

⁹² Bull. Soc. chim., (3) 11, pp. 407, 576, 1045.

⁹³ Comp. Pharm. Rev., 20, p. 401.

⁹⁴ Bull. Soc. chim., (3) 25, p. 981.

⁹⁵ See under dihydrochloride.

⁹⁶ Ann., 238, p. 82.

⁹⁷ Pharm. Journ., (3) 25, p. 1045.

⁹⁸ Ber. v. S. & Co., April 1898, p. 18.

⁹⁹ Arch. d. Pharm., 225, p. 515.

¹⁰⁰ Ber. v. S. & Co., Oct. 1898, Suppl. p. 33.

¹ Die Terpene, p. 175.

² Pharm. Archives, 4, p. 61; Proc. Amer. Pharm. Assoc., 49, p. 849,

that in this case the name cadinene was used as being synonymous with sesquiterpene.

Piper cubeba. Oil of Cubebs.

Soubeiran and Capitaine³ in 1840 examined cubeb oil and found it to consist largely of a sesquiterpene. By the action of hydrochloric acid they obtained a hydrochloride melting at 131°. This compound they called cubeb camphor, after the nomenclature then in use. This hydrochloride, like the original oil, was laevorotatory, but to a greater extent. It formed long, oblique, rectangular, tasteless and odorless prisms.

Later observers found the melting point of the dihydrochloride obtained from oil of cubebs at 118° and not 131° as reported by Soubeiran and Capitaine. The latter also state that it was readily soluble in cold alcohol, whereas all other observers especially mention its slight solubility in cold alcohol. Nevertheless, these authors in all probability had impure cadinene dihydrochloride under consideration.

In 1870 Schmidt⁴ obtained from the laevogyrate fraction of cubeb oil boiling about 250°, a dihydrochloride, $C_{15}H_{24} \cdot 2HCl$, melting at 120—125°. In 1877 he states that the dihydrochloride melts at 118°.⁵

Oglialoro⁶ in 1875 found in cubeb oil a laevogyrate "sesquiterben," $C_{15}H_{24}$, boiling at 264—265°, which yielded a hydrochloride melting at 118°. By heating with water to a high temperature, the hydrochloride was decomposed and yielded the original hydrocarbon. He also obtained a second hydrocarbon, boiling at a somewhat lower temperature, viz. 262—263°; it was less active optically and gave no hydrochloride. This latter hydrocarbon was probably an impure fraction of the same "sesquiterben" as even this distilled over at a temperature nearly ten degrees below the boiling point of pure cadinene. This is, however, by no means certain, as it may very easily happen that two sesquiterpenes occur in the oil, analogous to the occurrence of several terpenes in one oil. Later researches, however, do not mention this second sesquiterpene, although Schmidt⁷ in 1870 also mentioned "eine Modification des ätherischen Cubeben-

³ Journ. d. Pharm., 26, p. 76; Ann., 34, p. 828.

⁴ Arch. d. Pharm., 191, p. 21.

⁵ Ber., 10, p. 190.

⁶ Ber., 8, p. 1857.

⁷ Arch. d. Pharm., 191, p. 22.

öls" (sesquiterpene) which absorbs hydrochloric acid but does not combine with it.

Piper betle. Oil of Betel Leaves.

Eykman⁸ in 1889 isolated from Java betel oil a hydrocarbon boiling about 260°. Analysis and molecular weight determination indicated the formula C₁₅H₂₄. It had a specific gravity of 0.917 at 13°; n_D = 1.50400. The indices of refraction for the three hydrogen lines are also given. The molecular refraction indicates two double bonds. Bromine and hydrochloric acid in acetic acid produce a deep indigo-blue color. No chemical work is reported.

The chemists of Schimmel & Co.⁹ isolated a fraction from Siam betel oil boiling between 250—275°. It is described as having a pleasant tea-like odor and consists principally of cadinene ("cubebene") as was shown by the preparation of its dihydrochloride melting at 117—118°.

The betel oil investigated by Eykman differed somewhat in general composition from that of Schimmel & Co.,¹⁰ but the sesquiterpene found by Eykman is probably also identical with cadinene. The properties of cadinene and Eykman's sesquiterpene are given:

	B. p.	Sp. gr.	n _D
Sesquiterpene.....about 260° (Eykman)	0.917 (13°)	1.50400	
Cadinene..... 274—275° (Wallach)	0.918 (20°)	1.50647	

Although cadinene has been identified with certainty only in Siam oil, it is no doubt also present in the other commercial varieties.

ANONACEAE.

Cananga odorata. Ylang-Ylang and Cananga Oil.

Reychler¹¹ isolated from ylang-ylang oil a fraction boiling at 138—143° (20 mm.) which had the specific gravity 0.910 at 15° and index of refraction 1.50001 at 20°. The rotatory power was observed as +46.4° in a two decimeter tube, but the author is inclined to think that the rotation was —133.6°, as the original oil was strongly laevogyrate. This would make [α]_D = —73.4° for the hydrocarbon.

⁸ Ber. 22, p. 2736.

⁹ Ber. v. S. & Co. April 1889, p. 6; Journ. f. prakt. Chem., 89, p. 349.

¹⁰ See Ber. v. S. & Co., April 1890, p. 6.

¹¹ Bull. Soc. chim., (3) 11, pp. 407, 576.

This sesquiterpene yielded with hydrochloric acid a dihydrochloride melting at 117°.

In a second distillation¹² of the same oil the author obtained a corresponding fraction of decidedly different rotatory power. This fraction was obtained by distilling several times under atmospheric pressure. The boiling point was 250–255°, specific gravity 0.9125 at 18°; $n = 1.50380$; $[\alpha]_D = +6.8^\circ$ in a 9.1 p. c. alcoholic solution. Reychler thinks this dextro-rotation to be due to an inversion during the process of distillation under atmospheric pressure. Whether or not this dextrogyrate fraction gave a dihydrochloride like the laevo-gyrate fraction of the first distillation is not stated.

In a third communication Reychler¹³ reports on cananga oil. He isolated from it a fraction boiling at 189.5–145° (20 mm.). It had a specific gravity of 0.9024; $n = 1.50187$; $[\alpha]_D = -32.2^\circ$. This same substance when distilled under atmospheric pressure shows the following properties: specific gravity 0.9057; $n = 1.50103$; $[\alpha]_D = -1.25^\circ$. This shows that the rotatory power of the sesquiterpene suffers greatly by heat as already observed under ylang-ylang oil. No hydrochloride was prepared from this sesquiterpene, although it is probably identical with that found in ylang-ylang oil, namely, cadinene.

MONIMIACEAE.

Unknown *Monimiaceae*. Paracoto Bark Oil.

Wallach and Rheindorff¹⁴ showed the presence of cadinene in paracoto bark oil by the preparation of the dihydrobromide melting at 121°. From this they regenerated the sesquiterpene and prepared the dihydrochloride melting at 118° and having a rotation of -33.5° .

LAURACEAE.

Cinnamomum camphora. Oil of Camphor.

Schimmel & Co.¹⁵ isolated from the high boiling fractions of camphor oil, a sesquiterpene boiling at 260–270°, which yielded a hydrochloride melting at 117°, the same as that of the dihydrochloride of cadinene, "cubebene."

Sassafras officinalis. Sassafras Oil. Sassafras Leaf Oil.

Power and Kleber¹⁶ made a very thorough examination of an

¹² I. c., p. 582.

¹³ Bull. Soc. chim., (8) 11, p. 1045.

¹⁴ Ann., 271, p. 300.

¹⁵ Ber. v. S. & Co., April 1889, p. 9.

¹⁶ Pharm. Review, 14, p. 102.

authentic oil of both the bark and leaves. From each of these oils they obtained a small fraction (about 3 p. c. in the case of the oil from the bark) distilling between 260—270°. "In this the presence of cadinene was presumed, as it gave in glacial acetic acid solution with a trace of sulphuric acid the violet coloration which is characteristic for this sesquiterpene." No solid hydrochloride could, however, be obtained, so that the presence of this sesquiterpene must be left in doubt.

RUTACEAE.

Cusparia trifoliata. Angostura Bark Oil.

Beckurts and Troeger¹⁷ obtained from angostura bark oil a laevogyrate sesquiterpene, the hydrohalogen addition products of which agreed in melting point and rotation with the corresponding cadinene compounds. A sesquiterpene showing all the properties of cadinene could be generated from them.

Beckurts and Troeger also isolated a liquid sesquiterpene hydrate, $C_{15}H_{26}O$, which they called galipol (see this). This alcohol is inactive optically and has not been definitely characterized. The authors produced by heating it with acetic acid anhydride in a sealed tube to 170°, a dextrogyrate sesquiterpene, to which they gave the name of "galipene." The impure fractions of the oil, consisting of galipol and sesquiterpenes, gave the same hydrocarbon when subjected to this treatment. This socalled "galipene" gave a hydrochloride melting at 114—115° and a hydrobromide melting at 123°. These compounds were shown to be identical with the corresponding cadinene derivatives in a later report.¹⁸ The authors, therefore, discard the name of "galipene" for this dextrogyrate sesquiterpene and apply it to a third sesquiterpene found by them in the oil. This is inactive, optically, and not sufficiently well characterized to warrant the authors to apply a specific name to it.

That this socalled "galipene" is an inversion product is shown by the fact that the original oil is strongly laevogyrate (-50°) but when heated with acetic acid anhydride it becomes dextrogyrate ($18-20^\circ$). With phosphoric acid anhydride it is reduced to -10° . Distillation under atmospheric pressure alone will change the rotation from strongly laevogyrate to dextrogyrate.¹⁹ Reyhler²⁰ observed

¹⁷ Arch. d. Pharm., 285, pp. 518, 634; 286, p. 892.

¹⁸ Arch. d. Pharm., 286, p. 897.

¹⁹ Arch. d. Pharm., 286, pp. 404, 407.

²⁰ Bull. Soc. chim., (8) 11, pp. 582, 1045.

a similar inversion in the distillation of the sesquiterpene from ylang-ylang and cananga oils (see these) and found it to be due to the heat of distillation under atmospheric pressure. When distilled in a vacuum this inversion did not take place. Inasmuch as Beckurts and Troeger distilled almost entirely under atmospheric pressure, these different optical results can by no means be taken as evidence that chemical individuals were under consideration.

Citrus bigaradia. Oil of Petitgrain.

According to Semmler and Tiemann²¹ petitgrain oil contains a high-boiling sesquiterpene. Charabot and Pillet²² state that the residue above 232° deposited a crystalline substance, the quantity of which was too small to analyse. The liquid portion of this residue gave the color reaction for cadinene with glacial acetic acid and sulphuric acid, thus indicating the possible presence of this sesquiterpene.

Amyris balsamifera. West Indian Sandalwood Oil.

H. v. Soden²³ reports the presence of sesquiterpenes in West Indian sandalwood oil. This sesquiterpene fraction Heine & Co.²⁴ call "amyrene" after the name of the genus yielding the oil. In view of Deussen's work, however, they suggest that amyrene is d-cadinene, although Deussen²⁵ obtained all three hydrohalogen derivatives of l-cadinene from the oil. The dihydrochloride, dihydriodide and dihydribromide, agreed in melting point, composition and optical rotatory power with the corresponding derivatives of cadinene determined by Wallach. A peculiarity is that the oil, and also the sesquiterpene according to Heine & Co., is dextrogyrate, whereas laevo- gyrate cadinene derivatives are obtained from it. This is similar to the results obtained by Beckurts and Troeger²⁶ with angostura oil.

BURSERACEAE.

Boswellia carterii and other species. Oil of Olibanum (Frankincense).

Wallach and Walker²⁷ mention cadinene as occurring in oil of olibanum.

²¹ Ber., 25, p. 1186.

²² Bull. Soc. Chim., 21, p. 74.

²³ Pharm. Ztg., 45, pp. 229, 878.

²⁴ List of products exhibited at Paris, 1900.

²⁵ Arch. d. Pharm., 288, p. 149.

²⁶ Arch. d. Pharm., 285, pp. 518, 684; 286, p. 392.

²⁷ Ann., 271, p. 297.

MELIACEAE.

Cedrela species. Oil of Cedrela Wood.

According to Schimmel & Co.²⁸ Cuban cedrela wood oil contains large amounts of cadinene, as was shown by the preparation of the dihydrochloride melting at 118°. The rotation of the original oil was, however, dextrogyrate, $\alpha_D = +18^\circ 6'$.

Punta Arenas (Costa Rica) cedrela wood oil likewise consists principally of a sesquiterpene yielding cadinene dihydrochloride melting at 118°.²⁹ The rotation of this oil was to the left, $\alpha_D = -5^\circ 53'$.

The other commercial varieties of cedrela wood oils, Corinto, La Plata, and Porto Alegre are, like the foregoing oils, light blue or yellowish in color and probably also consist largely of sesquiterpenes.

DIPTEROCARPACEAE.

Dryobalanops camphora.

Lallemand³⁰ in 1860 found in the oil of *Dryobalanops camphora* a sesquiterpene which boiled between 255 and 270°, the larger amount distilling at 260°. The specific gravity changed in this interval of temperature from 0.90 to 0.921 at 20°, and the rotation changed from slightly laevo- to dextrogyrate and increased up to the fraction going over at 265°, when it again decreased, the portion distilling at 270° being inactive. With hydrochloric acid it yields a crystalline compound, $C_{15}H_{24} \cdot 2HCl$, melting at 125°. This compound rotated the ray of polarized light always to the left, no matter whether it was obtained from a dextro or a laevorotatory portion of the oil.

Lallemand regenerated the sesquiterpene from this dihydrochloride by treatment with lead oxide or mercuric oxide at 100°, or saponification with alcoholic potassa. This regenerated hydrocarbon boiled at 260°, was strongly laevogyrate and combined again with hydrochloric acid to yield the same dihydrochloride. Although the melting point of this dihydrochloride as reported is rather high for cadinene dihydrochloride, it is nevertheless very probable that Lallemand had this compound under consideration.

UMBELLIFERAE.

Ferula asa foetida and other species of

Ferula and *Peucedanum*. Oil of Asafetida.

Cadinene does not occur as such in asafetida oil, but is obtained from an oxygenated constituent by repeated treatment with sodium.

²⁸ Ber. v. S. & Co., April 1892, p. 41.

²⁹ I. c.

³⁰ Ann. chim. phys., (8) 57, p. 401; Ann. 114, p. 198.

This oxygenated constituent was isolated from the oil by Semmler⁸¹ and had a boiling point of 113–145° (9 mm.); $d_{22}^{\circ} = 0.9639$; $a_D = -16^{\circ}$. Analyses corresponded to the formula $(C_{10}H_{16}O)_n$. This oxygenated constituent gave by repeated distillation with metallic sodium an oil which corresponded in composition and vapor density to a sesquiterpene. It had the following properties: an odor resembling lavender; b. p. 123° (9 mm.); $d_{18}^{\circ} = 0.9241$. With hydrochloric acid gas it yielded a dihydrochloride having the melting point 116°, nearly identical with that found for cadinene dihydrochloride.

Ferula rubricaulis and other species. Oil of Galbanum.

Oil of galbanum is mentioned by Wallach⁸² as yielding large amounts of cadinene dihydrochloride.

LABIATAE.

Mentha piperita. American Oil of Peppermint.

From the high boiling fractions of American peppermint oil, Schimmel & Co.⁸³ obtained a fraction boiling about 260°, which yielded, when treated with hydrochloric acid gas, a solid, crystalline dihydrochloride, melting at 118°, identical with cadinene dihydrochloride.

English oil of peppermint also contains a sesquiterpene, but no hydrochloride was prepared.⁸⁴

Pogostemon patchouli. Oil of Patchouly.

Oil of patchouly is mentioned by Wallach⁸⁵ as containing large quantities of cadinene. The fraction 270–280° yielded a large amount of the dihydrochloride.

COMPOSITAE.

Solidago canadensis. Oil of Golden Rod.

According to Schimmel & Co.⁸⁶ cadinene is found in the oil distilled from *Solidago canadensis*. They do not state on what evidence the conclusion is based.

Artemisia absinthium. Oil of Wormwood.

The presence of cadinene in fraction 260–280° was shown by

⁸¹ Arch. d. Pharm., 229, p. 15; Ber., 28, p. 3532; 24, p. 80.

⁸² Ann., 238, p. 81.

⁸³ Bericht S. & Co., April 1894, p. 42.

⁸⁴ Pharm. Journ., (8) 11, p. 220; Arch. d. Pharm., 218, p. 222.

⁸⁵ Ann., 238, p. 81.

⁸⁶ Bericht S. & Co., April 1897, p. 53.

Schimmel & Co.³⁷ by the formation of its dihydrochloride melting at 117—118°.

Preparation.

Cadinene has not been isolated in a pure state from any of the oils, the socalled cadinene fractions of these oils in fact, showing widely different properties. These fractions serve for the preparation of the dihydrochloride of cadinene as will be described below. From the purified dihydrochloride, the hydrochloric acid is again split off and pure cadinene regenerated.

As early as 1860 Lallemand³⁸ regenerated the hydrocarbon from the dihydrochloride by treatment with lead oxide or mercuric oxide at 100°, or saponification with alcoholic potash. Lallemand determined the boiling point of the regenerated hydrocarbon at 260°, found it to be strongly laevogyrate and to yield the same hydrochloride when treated with hydrochloric acid gas. Oglialoro³⁹ in 1875 attempted to prepare the pure hydrocarbon by heating the hydrochloride with water to 170—180° for some time. He obtained a hydrocarbon boiling, when rectified, between 264—265° and again yielded the same dihydrochloride melting at 118°.

In 1887 Wallach⁴⁰ subjected the dihydrochloride to a more detailed study. The dihydrochloride had been obtained from fraction 260—280° as described under cadinene dihydrochloride, and from this the hydrocarbon was regenerated. According to this investigator the hydrochloric acid can be split off by two methods⁴¹, either of which is more satisfactory than the methods employed by Lallemand or Oglialoro.

1. With aniline. 20 g. of the pure hydrochloride are warmed with twice this weight of aniline for a few minutes, until the formation of aniline hydrochloride takes place. When the reaction is complete the excess of aniline is removed by shaking with hydrochloric acid. The hydrocarbon is then distilled with steam and after drying with solid potassium hydrate, it is rectified by distillation. Almost the entire amount passes over from 274—275°.

2. With anhydrous sodium acetate. A mixture of 20 g. of the pure dihydrochloride with 20 g. of anhydrous sodium acetate, are treated with 80 cc. of glacial acetic acid, and heated in a flask

³⁷ Bericht S. & Co., April 1897, p. 51.

³⁸ Ann. chim. phys., (8) 57, p. 401; Ann., 114, p. 198.

³⁹ Gazz. chim., 5, p. 567; Ber., 8, p. 1857.

⁴⁰ Ann., 1288, p. 78.

⁴¹ Ann., 288, pp. 80, 84.

provided with a reflux condenser. At first a clear solution results, but after a few minutes the separation of sodium chloride begins and in less than half an hour the reaction is complete. On cooling, a part of the hydrocarbon separates out at the surface and by the addition of water, the entire amount of the sesquiterpene separates. By washing with water, or better by shaking with some solution of sodium hydrate and subsequent distillation with steam, the cadinene is obtained in a pure state. After drying, the cadinene distills constant at 274—275° as with the first method.

Physical Properties.

The physical constants given under this heading apply only to the regenerated cadinene and not to any so-called cadinene fractions obtained from volatile oils. For the properties of these fractions the respective oils must be consulted under the heading of occurrence.

As already mentioned both Lallemand and Oglialoro had the regenerated sesquiterpene in hand. The boiling points given by both these investigators is low, Lallemand's being 260° and Oglialoro's 264—265°, whereas Wallach found it to be 274—275°. Wallach⁴² explains this difference of ten degrees in the boiling point by the fact that the method used by Oglialoro could hardly have separated all of the hydrochloric acid and that the hydrocarbon under consideration was not pure. Moreover, Wallach's results are all stated for a corrected boiling point and for this reason would be somewhat higher. The same argument will doubtless apply to Lallemand's results, whose hydrochloride could not have been pure to start with, as it melted at 125° instead of 118°.

The physical constants as found by Wallach and Conrady⁴³ are as follows: B. p. 274—275°; $d_{16}^{\circ} = 0.921$, $d_{20} = 0.918$; $n_D = 1.50647$; $[\alpha]_D = -98.56^{\circ}$ in a 13.05 p. c. chloroformic solution.

Beckurts and Troeger⁴⁴ regenerated from the hydrobromide obtained from angostura bark oil a sample of cadinene which was evidently less pure than that obtained by Wallach. Its physical constants were: B. p. 264—269° (uncorr.); $d_{19}^{\circ} = 0.9240$; $n_{D19} = 1.50790$; $[\alpha]_D = -88^{\circ} 37'$.

Grimal* obtained from the oil of *Cedrus atlantica* a hydrochloride from which he regenerated the dextro variety of cadinene. This re-

⁴² Ann., 238, p. 80, footnote.

⁴³ Ann., 238, p. 85; 252, p. 150; 271, p. 297.

⁴⁴ Arch. d. Pharm., 286, p. 396.

* Compt. rend. 185, pp. 582, 1057.

generated d-cadinene had the following properties: b. p. 274—275°; $d_{15}^{\circ}=0.9212$; $n_D = 1.5094$; $[\alpha]_D = +47^\circ 55'$.

The molecular refraction of cadinene calculated from the index of refraction indicates two double bonds.

Pure cadinene is a colorless, rather limpid liquid, having an odor that is not unpleasant. It shows a great tendency to resinify when exposed to the air, the liquid becoming very viscous in a few days. Schreiner and Kremers⁴⁵ found that if cadinene is kept in contact with solid caustic potash, it will retain its original characteristics for several months.

Cadinene is soluble with difficulty in alcohol and glacial acetic acid, but dissolves readily in ether.

Chemical Properties and Derivatives.

Cadinene yields with the hydrohalogens well characterized addition products which retain the laevo-rotation of the pure cadinene, but are less active. The dihydrohalogen addition products are quite stable and are readily crystallizable, except the dihydriodide which is decomposed by alcohol and can only be obtained in a pure form by crystallizing from anhydrous solvents. According to Deussen⁴⁶ the stability decreases from the hydrochloride to the hydriodide when heat is applied.

Cadinene also yields a nitrosate and a nitrosochloride. On oxidation with chromic acid it yields many of the lower fatty acids, which are volatile with water vapor. When allowed to drop slowly into cold fuming nitric acid, a lively reaction takes place and each drop is dissolved. By pouring into water and washing, a yellow, solid compound, which is soluble in caustic alkali and cannot be crystallized, is obtained.

Cadinene gives a very fine color reaction when it is dissolved in much chloroform and drops of sulphuric acid are added. The chloroform becomes green, then blue, and on heating changes to red. The reaction is still more striking when the cadinene is dissolved in much acetic acid and conc. sulphuric acid is added drop by drop. This color reaction is only very faintly shown by the pure, recently distilled hydrocarbon, while resinification is very favorable to it. It may be of interest to add that the cadinene preserved for several

⁴⁵ Pharm. Archives, 2, p. 299; Proc. Amer. Pharm. Assoc., 47, p. 180.

⁴⁶ Arch. d. Pharm., 238, p. 155.

years with solid caustic potash as above stated, gave this reaction so faintly that it could scarcely be recognized, whereas another sample, not so treated and completely resinified, gave an intense reaction. This color reaction is therefore not characteristic of the pure sesquiterpene, but depends on the products of oxidation, accompanying it as an impurity. The reaction is very useful, however, as an indication of the presence of this sesquiterpene, but can hardly be accepted as a proof.

According to Wallach⁴⁷ cadinene appears to be changed by continued heating with dilute sulphuric acid.

Cadinene dihydrochloride, $C_{15}H_{24}2HCl$. The dihydrochloride was first obtained by Soubeiran and Capitaine⁴⁸ from cubeb oil in 1840 and was called by them, cubeb camphor, melting at 181°. In 1860 Lallemand⁴⁹ obtained a dihydrochloride melting at 125° from the oil of *Dryabalanops camphora*. Schmidt⁵⁰ in 1870 and 1877 and Oglialoro⁵¹ in 1875 again obtained this compound from cubeb oil. Both report the melting point of 118°.

Wallach⁵² in 1887 obtained this dihydrochloride from the high boiling fractions of cubeb, patchouly, galbanum, savin and cade oils. According to Wallach the dihydrochloride is best prepared from oil of cade as follows:

Crude oil of cade is distilled with steam under pressure and the distillate freed from phenols by shaking with alkali. The nonphenols are then dried over solid caustic potash and rectified. Fraction 260—280° is diluted with twice its volume of ether, saturated with dry hydrochloric acid gas and allowed to stand for several days. At the end of this time, the ether is distilled off on a water bath or allowed to evaporate spontaneously. From the residue large amounts of the dihydrochloride crystallize out. The crystals are collected on a force filter and washed with cold alcohol. By recrystallization from hot ethyl acetate and washing with alcohol, the substance is obtained in small but pure crystals. By allowing it to crystallize slowly from a solution in ordinary ether, the dihydrochloride can be obtained in well developed rhombic hemihedral prisms.⁵³

Another method, which is especially well suited for preparing

⁴⁷ Ann., 271, p. 297.

⁴⁸ Journ. d. Pharm., 26, p. 76; Ann., 84, p. 823.

⁴⁹ Ann. chim. phys. (8) 57, p. 401; Ann., 114, p. 193.

⁵⁰ Arch. d. Pharm., 191, p. 21; Ber., 10, p. 190.

⁵¹ Guzz. chim., 5, p. 467; Ber., 8, p. 1357.

⁵² Ann., 238, p. 78.

⁵³ For crystallographic measurements by Hintze see Ann., 288, p. 88.

small quantities is to add to a solution of the hydrocarbon in acetic acid, some fuming hydrochloric acid, or better a solution of the gas in acetic acid. After shaking for a short time the dihydrochloride crystallizes out.

Troeger and Feldmann⁵⁴ have met with difficulty in preparing the dihydrochloride from oil of cade. This same difficulty was experienced in this laboratory and has already been discussed under oil of cade in the section on occurrence. The difficulty is due either to the fact that the sesquiterpene yielding the dihydrochloride is not always present in the oil, or else it has undergone changes during distillation as Reyehler⁵⁵ has shown in the case of ylang-ylang and cananga oils.

In order to avoid the application of direct heat to the oil, Cathelineau and Haussner⁵⁶ proceed as follows:

Oil of cade is freed from phenols with caustic soda solution and the nonphenols distilled with steam. This distillate, without previous fractionation, is then mixed with three times its volume of 90 p. c. alcohol. The oil is only slightly soluble and settles to the bottom. A very rapid current of dry hydrochloric acid gas is then passed into the cooled mixture until saturated, when it is allowed to stand for twenty-four hours in a cool place. At the end of this time the oil at the bottom will be found to have formed a magma of crystals. These are collected and washed with a little alcoholic hydrochloric acid and finally with absolute alcohol. They may be purified by recrystallization from a little hot absolute alcohol.

The pure dihydrochloride is obtained in white crystals which are sparingly soluble in cold alcohol, more so in ether and in hot alcohol. It is readily soluble in hot ethyl acetate from which it crystallizes on cooling.

Cadinene dihydrochloride melts at 117–118° and according to Wallach and Conrady,⁵⁷ $[\alpha]_D = -36.82^\circ$ in a 7.212 p. c. chloroformic solution. Beckurts and Troeger⁵⁸ found $[\alpha]_D = -37.3^\circ$ in a 7.91 p. c. chloroformic solution, and Deussen⁵⁹ reports $[\alpha]_D = -36.65^\circ$ in a 3.358 p. c. chloroformic solution. These three samples

⁵⁴ Arch. d. Pharm., 236, p. 692.

⁵⁵ Bull. Soc. chim., (3) 11, pp. 407, 576, 1045.

⁵⁶ Bull. Soc. chim., (3) 25, p. 981.

⁵⁷ Ann., 252, p. 150.

⁵⁸ Arch. d. Pharm., 236, p. 898.

⁵⁹ Arch. d. Pharm., 238, p. 158.

of dihydrochloride had been obtained from cade, angostura bark and West Indian sandalwood oils respectively.

By treating with aniline or anhydrous sodium acetate in glacial acetic acid solution, the cadinene can be regenerated as was mentioned above. This regenerated cadinene again yields the same dihydrochloride when treated as above, or with a solution of hydrochloric acid gas in glacial acetic acid.

The d-cadinene dihydrochloride obtained by Grimal* from the oil of *Cedrus atlantica* had the following properties: m. p. 117–118°; $[\alpha]_D = +8^\circ 55'$ in chloroform solution and $+25^\circ 40'$ in acetic ether solution.

According to Wallach and Walker⁶⁰ cadinene dihydrochloride, when heated with hydriodic acid (sp. gr. 1.96) for 15 hours to 180–200°, yields a saturated hydrocarbon, $C_{15}H_{28}$, having the following properties: b. p. 257–260°; $d_{18} = 0.872$; $n_D = 1.47439$.

Cadinene dihydriodide, $C_{15}H_{24}2HBr$. This compound can be prepared in a manner analogous to that used in the preparation of the dihydrochloride. According to Wallach⁶¹ it forms very readily when a solution of cadinene in glacial acetic acid is treated with fuming hydrobromic acid. Deussen⁶² prepared it by shaking the hydrocarbon with twice its volume of ether saturated with hydrobromic acid, and Beckurts and Troeger⁶³ by shaking with ten times its volume of a saturated solution of hydrobromic acid in glacial acetic acid. The dihydriodide can be recrystallized from ethyl acetate. It forms white crystals melting at 124–125°. According to Wallach and Conrady,⁶⁴ $[\alpha]_D = -36.13^\circ$ in a 7.227 p. c. chloroformic solution. Beckurts and Troeger⁶⁵ found $[\alpha]_D = -36.17^\circ$ in a 4.62 p. c. chloroformic solution and Deussen⁶⁶ -36.26° in a 3.23 p. c. solution in the same solvent.

Grimal† prepared d-cadinene dihydriodide, but does not give its rotatory power. M. p. 124–125°.

Cadinene dihydriodide, $C_{15}H_{24} \cdot 2HI$. According to Wallach⁶⁷ this forms very readily when the pure hydrocarbon, dissolved in

* Compt. rend. 135, pp. 582, 1057.

⁶⁰ Ann., 271, p. 295.

⁶¹ Ann., 288, p. 86.

⁶² Arch. d. Pharm., 288, p. 153.

⁶³ Arch. d. Pharm., 285, p. 641.

⁶⁴ Ann., 252, p. 151.

⁶⁵ Arch. d. Pharm., 236, p. 398.

⁶⁶ Arch. d. Pharm., 238, p. 158.

⁶⁷ Compt. rend. 135, pp. 582, 1057.

[†] Ann., 288, p. 86.

several times its volume of glacial acetic acid, is shaken with fuming hydriodic acid. A heavy oil forms which soon crystallizes. Deussen⁶⁸ used ether saturated with hydriodic acid. It is best purified by spreading on a porous plate until thoroughly dry and then crystallizing from a little hot petroleum ether, or ethyl acetate. Alcohol decomposes it readily.

The dihydriodide forms white woolly needles, melting at 105–106° with decomposition. According to Wallach and Conrady⁶⁹ $[\alpha]_D = -48.00^\circ$ in a 5.568 p. c. chloroformic solution.

Cadinene nitrosochloride, $C_{15}H_{24}NOCl$. Schreiner and Kremers⁷⁰ prepare this compound by dissolving one part of pure cadinene in three parts of glacial acetic acid and one part of ethyl nitrite, then cooling this solution in a freezing mixture. To the cold solution is added very gradually one part of a saturated solution of dry hydrochloric acid gas in glacial acetic acid. The solution becomes dark green and after the addition of a little alcohol and standing for about two hours, the nitrosochloride separates out. The compound is washed with cold alcohol and dried on a porous plate.

Cadinene nitrosochloride is a white powder melting at 93–94° with decomposition.

Cadinene nitrosate, $C_{15}H_{24} \cdot N_2O_4$. According to Schreiner and Kremers⁷¹ the nitrosate is prepared as follows: One part of pure cadinene is dissolved in three parts of glacial acetic acid and one part of ethyl nitrite. This is then strongly cooled in a freezing mixture and a solution of one part of conc. nitric acid in one part of glacial acetic acid gradually added. After standing a few minutes, the turbid mixture is treated with an equal volume of ordinary alcohol, which will cause a dense precipitate of the nitrosate. This is collected, washed with cold alcohol and dried on a porous plate.

Cadinene nitrosate is a light, white powder, sparingly soluble in cold alcohol, more readily in hot alcohol and in benzol, but has not been recovered in a crystalline form from these solvents. It melts between 105 and 110° with decomposition.

Molecular weight determinations by the cryoscopic method, using benzol as solvent, show it to be a bisnitroso compound ($C_{15}H_{24} \cdot N_2O_4)_2$.⁷²

⁶⁸ Arch. d. Pharm., 238, p. 154.

⁶⁹ Ann., 252, p. 151.

⁷⁰ Pharm. Archives, 2, p. 800; Proc. Amer. Pharm. Assoc., 47, p. 181.

⁷¹ Pharm. Archives, 2, p. 299; Proc. Amer. Pharm. Assoc., 47, p. 180.

⁷² Upjohn, Thesis 1899, University of Wisconsin.

Oxygenated Compounds Yielding Cadinene or its Derivatives.

Several sesquiterpene hydrates and other oxygenated compounds of high molecular weight are found in volatile oils accompanying cadinene, but whether all of these will yield cadinene or its derivatives is still an open question. In many instances this appears not to be the case. So far only one sesquiterpene hydrate, galipol, and another body ($C_{10}H_{16}O$)_n, the nature of which is unknown, have definitely yielded cadinene derivatives. H. v. Soden⁷³ and Rojahn are of the opinion that the alcohol $C_{15}H_{25}OH$ from West Indian sandalwood oil also yields cadinene.

Semmler⁷⁴ is of the opinion that the high boiling blue fractions obtained in the distillation of many oils, and variously designated as coerulin, azulene, etc., will yield cadinene by treatment with sodium, similar to the reaction noticed by him for the compound ($C_{10}H_{16}O$)_n.

Oxygenated compound, ($C_{10}H_{16}O$)_n, from asafetida oil. Semmler⁷⁵ isolated from asafetida oil a compound ($C_{10}H_{16}O$)_n, which by repeated treatment with sodium yielded a sesquiterpene, the dihydrochloride of which agreed in its properties with cadinene dihydrochloride. This oxygenated body had the following properties: b. p. 133—145° (9 mm.); $d_{20}^{\circ} = 0.9639$; $\alpha_D = -16^{\circ}$.

The properties of the sesquiterpene obtained from it were: b. p. 128° (9 mm.); $d_{15}^{\circ} = 0.9241$. The melting point of the dihydrochloride was 116°.

Sesquiterpene hydrate, $C_{15}H_{25}OH$, from angostura bark oil. Galipol. Beckurts and Troeger⁷⁶ isolated from angostura bark oil a not well characterized sesquiterpene hydrate, which on dehydration gave a dextrogyrate sesquiterpene yielding hydrohalogen derivatives identical in all their properties⁷⁷ with the corresponding cadinene derivatives. The physical properties of galipol were as follows: b. p. 260—270°; $d_{20}^{\circ} = 0.9270$; $n_D = 1.50624$; optically inactive.

The physical properties of the sesquiterpene were: b. p. 256—260°; $d_{20}^{\circ} = 0.9110$; $\alpha_D = +18^{\circ}$.

It may be mentioned that Beckurts and Nehring⁷⁸ in 1891 found

⁷³ Pharm. Ztg., 45, p. 878.

⁷⁴ Arch. d. Pharm., 228, p. 20.

⁷⁵ Arch. d. Pharm., 229, p. 15.

⁷⁶ Arch. d. Pharm., 235, p. 526.

⁷⁷ Arch. d. Pharm., 236, p. 897.

⁷⁸ Arch. d. Pharm., 229, p. 612.

that the fraction of angostura oil, boiling above 240°, solidified when cooled in a mixture of sodium sulphate and hydrochloric acid. This fraction must have contained the galipol, but the later articles of Beckurts and Troeger make no mention of this property to solidify when cooled.

Alcohol $C_{15}H_{23}OH$, from West Indian sandalwood oil. In 1900 v. Soden⁷⁹ isolated from West Indian sandalwood oil an alcohol for which he proposed the name amyrol. In a later communication v. Soden and Rojahn⁸⁰ report amyrol as consisting of two alcohols, the higher boiling one having the composition $C_{15}H_{25}OH$, and the other $C_{15}H_{23}OH$. This lower boiling compound is optically inactive. Both the alcohols yield sesquiterpenes when treated with mineral acids. The sesquiterpene from the lower boiling alcohol, $C_{15}H_{23}OH$, the authors suspect to be l-cadinene, but they prepared no derivative to confirm their belief, nor do they give the properties of the generated hydrocarbon.

5. Calamene.

By boiling with sodium, Kurbatow⁸¹ isolated from the high boiling fractions of calamus oil a hydrocarbon $C_{15}H_{24}$, having the following properties:

B. p. 255—258°; $d_0^{\circ} = 0.942$, $d_{14}^{\circ} = 0.9323$.

It is described as a colorless, odorless oil, which would not combine with hydrochloric acid.

Gladstone⁸² in 1872 called this sesquiterpene calamene.

Oil of Japanese calamus from *Acorus spuriosus* also contains a sesquiterpene which has not been examined.⁸³

6. Caparrapene.

Tapia⁸⁴, in 1898, isolated from caparrapi oil an alcohol which he recognized as a sesquiterpene hydrate. From this hydrate, which he called caparrapiol, he obtained by dehydration the sesquiterpene caparrapene.

⁷⁹ Pharm. Ztg., 45, p. 229.

⁸⁰ Pharm. Ztg., 45, p. 878.

⁸¹ Ann., 173, p. 4.

⁸² Pharm. Journ., 81, p. 687.

⁸³ Bericht S. & Co., April 1889, p. 7.

⁸⁴ Bull. Soc. chim., (3), 19, p. 688.

Preparation.

Caparrapiol is treated with its own weight of phosphoric acid anhydride. An energetic reaction takes place and when this is ended, the hydrocarbon formed is distilled off at ordinary pressure, collecting the fraction 240—250° separately. This fraction is again treated with phosphoric acid anhydride and rectified. Tapia does not give the boiling point of this rectified product and we must, therefore, conclude that he again collected fraction 240—250°.

The dehydration may also be effected by heating the caparrapiol with twice its weight of acetic acid anhydride for two hours. The oily liquid, separated by the addition of water, well washed and dried with anhydrous sodium sulphate, is distilled under diminished pressure.

Hydrochloric acid and zinc chloride also remove water from caparrapiol, but besides caparrapene, a large number of polymeric substances are formed.

Physical Properties.

Caparrapene is a colorless liquid which becomes yellow on exposure to air and is less soluble in alcohol and glacial acetic acid than caparrapiol. Tapia found the following physical constants:

B. p. 240—260°; $d_{16}^{\circ} = 0.9019$; $[\alpha]_D = -2.21^{\circ}$; $n = 1.4953$.

Chemical Properties.

The chemical study of caparrapene is restricted to a color reaction and the preparation of a minute quantity of a hydrochloride. The color reaction consists in dissolving the sesquiterpene in glacial acetic acid and adding a trace of sulphuric acid. A rose color develops which passes into an intense violet.

Di-hydrochloride. Tapia prepared this derivative by passing dry hydrochloric acid gas into a solution of caparrapene in glacial acetic acid. The crude liquid hydrochloride, when washed and dried, corresponded with the formula $C_{15}H_{24} \cdot 2HCl$. After standing for some time small crystals separated, which were recrystallized from alcohol. They formed white hexagonal plates which strongly polarize light and melt at 83°. The amount was unfortunately too small for further study.

Caparrapiol, the sesquiterpene hydrate yielding caparrapene. Tapia separated the caparrapiol, which is the principal constituent of caparrapi oil, by fractional distillation under diminished pressure.

It is a colorless, mobile liquid, having the odor of the oil. It is miscible with alcohol, and with a mixture of glacial acetic and sulphuric acids it gives a red color. Dehydrating agents give rise to the sesquiterpene caparrapene described above.

Tapia found the following constants for the impure caparrapiol separated by fractional distillation from the oil:

B. p. 180–185° (40–45 mm.); $d_{15}^{\circ} = 0.8915$; $[\alpha]_D = 10.31^{\circ}$;
 $n = 1.4811$.

The caparrapene above described was prepared from this fraction.

7. Caryophyllene.

Synonyms.

The class names in the older nomenclatures, such as,

- Paracopaiba oil,
- Indifferent oil of cloves,
- Camphene of clove oil,
- Paracamphene,
- Cedrene,
- Sesquiterebene,
- Sesquiterebenthene,
- Sesquiterpene,
- Diterpene (erroneously),

and the specific names,

- Copaivene,
- Caryophyllene.

Caryophyllene, like cadinene, is referred to in the early literature, before it was characterized, under the general class names of camphene, paracamphene, sesquiterpene etc., associated with the name of the oil in which it occurs, for instance, "Nelken camphen"⁸⁵ (1858). It is also called by the name of the oil, for instance "Paracopaivaöl"⁸⁶

⁸⁵ Brüning, Ann., 104, p. 202; Williams Canstatts Jahresb. d. Pharm., 1858, p. 187.

⁸⁶ Posselet, Ann., 69, p. 69.

(1849), "Indifferent oil of cloves"⁸⁷ (1860). The sesquiterpene of copaiba balsam oil was formerly considered as a diterpene, because its vapor density, determined by Dumas' or Hoffmann's method, was found to agree with the formula $C_{20}H_{32}$. Blanchet⁸⁸ in 1833 used the term "salzaures Copaiyl" and Soubeiran and Capitaine⁸⁹ in 1839 refer to the sesquiterpene of copaiva oil as copaivene. Wallach⁹⁰ in 1892 characterized the sesquiterpene of clove oil and proposed for it the name of caryophyllene, after the genus name of the plant yielding clove oil.

History and General Discussion.

Caryophyllene is perhaps at present the best characterized of the known sesquiterpenes. It appears to be much less widely distributed than cadinene, but occurs, nevertheless, in oils widely separated botanically. Moreover, caryophyllene actually exists in these oils as such, whereas with cadinene, as was pointed out, this is a doubtful point.

The history of caryophyllene is closely connected with the development of the chemical study of clove and copaiba balsam oils. The former consists mainly of eugenol and caryophyllene, the latter is said to consist principally of this sesquiterpene. In the preparation of eugenol from oil of cloves, the hydrocarbon was usually obtained as a side product, but not closely studied. Ettling⁹¹ in 1834, pointed out the presence of a hydrocarbon in clove oil, and since then, Böckmann,⁹² 1838, Brüning,⁹³ 1857, Williams,⁹⁴ 1858, and Church,⁹⁵ 1875, have had the hydrocarbon in hand, without, however, adding anything to its chemical study, further than to state that no crystalline hydrochloride could be obtained.

As stated above, oil of copaiba balsam consists chiefly of a sesquiterpene which Wallach⁹⁶ in 1892 identified as caryophyllene. The

⁸⁷ Gmelin, *Handbook of Chem.*, Engl. ed. 4, 14, p. 285.

⁸⁸ Ann., 7, p. 156.

⁸⁹ Ann., 34, p. 322.

⁹⁰ Ann., 271, p. 287.

⁹¹ Ann., 9, p. 68.

⁹² Ann., 27, p. 155.

⁹³ Ann., 104, p. 202.

⁹⁴ Chem. Gaz., 1858, p. 170; Chem. Centralbl., 29, p. 495.

⁹⁵ Journ. Chem. Soc., 28, p. 113.

⁹⁶ Ann., 271 p. 285.

results of the earlier chemical studies are not wholly in agreement with this. Blanchet⁹⁷ in 1833 obtained from the oil a hydrochloride melting at 54° and having the composition $C_{10}H_{16} \cdot 2HCl$. Soubeiran and Capitaine⁹⁸ in 1840 confirmed this formula, but gave the melting point at 77°. Later investigators failed to get a hydrochloride from the oil. Until 1899 the dihydrochloride of caryophyllene had not been prepared in a crystalline condition, but Schreiner and Kremers⁹⁹ showed that it could be obtained in the form of crystals melting at 69—70°. Whether these early investigators had this same dihydrochloride in hand is very doubtful from their analyses, but this, as well as their widely different melting points may possibly have been due to a very impure condition of their product.

Another discrepancy is the fact that Strauss¹⁰⁰, Brix¹ and also Levy and Engländer² found the vapor density to agree with the formula $C_{20}H_{32}$. This, however, may be explained by the changes which these high boiling sesquiterpenes suffer when vaporized. The specific gravity of the fractions of copaiba balsam oil as given by these investigators is usually somewhat low for caryophyllene, but the boiling point, and also the rotatory power when given, agree fairly well with impure caryophyllene. There are, however, a number of commercial varieties of copaiba balsam and the widely varying rotatory power of different samples of the oil, from —7° to —35°, would seem to indicate the presence of other hydrocarbons or possibly oxygenated constituents in some of these. This assumption would explain many of the discrepancies mentioned above, and possibly also some of the results obtained by oxidizing the oil, as will be mentioned below. Moreover, Umney³ in 1893 failed to get a hydrate from fraction 264° of African copaiba oil by the method used by Wallach for caryophyllene. The oil, moreover, was dextrogyrate 20° 42' while the other varieties are laevogyrate. The application of the nitrosite reaction of Schreiner and Kremers to these different varieties of copaiba oil, would no doubt clear up many of these

⁹⁷ Ann., 7, p. 154.

⁹⁸ Journ. de Pharm., 26, p. 565.

⁹⁹ Pharm. Archives, 2, p. 296; Proc. Amer. Pharm. Assoc., 47, p. 178.

¹⁰⁰ Ann., 148, p. 148.

¹ Ber., 14, p. 2267.

² Ann., 242, p. 189.

³ Pharm. Journ. 58, p. 215.

doubtful points. The blue nitrosite and the nitrosobenzylamine derivatives are far better suited for the detection and identification of caryophyllene than the hydrate; for the failure to obtain the hydrate is not always a good proof of the absence of the hydrocarbon.

The oxidation products obtained from copaiba balsam oil by the various workers also indicate that different hydrocarbons, or mixtures of these with other unknown compounds were present in the oils examined.

In 1892 Wallach and Walker⁴ prepared from the hydrocarbon of clove and copaiba balsam oil, a nitrosochloride and the well crystallized hydrate, alluded to above, by treatment with glacial acetic acid, sulphuric acid and water. This hydrate when pure melted at 96° and thus gave a means for the characterization and identification of this hydrocarbon, for which the name of caryophyllene was proposed. Later Wallach⁵ also prepared the nitrosate and nitrol-piperidene base.

Schreiner and Kremers⁶ in 1899 still further characterized caryophyllene by the preparation of a crystalline dihydrochloride, the blue nitrosite mentioned above, and two white modifications and two benzylamine compounds, so that caryophyllene is now the best characterized representative of the group of sesquiterpenes.

Caryophyllene has not been regenerated from any of its derivatives. Wallach⁷ attempted to regenerate it from the hydrate, but obtained an isomeric hydrocarbon, which he called clovene. Schreiner and Kremers⁸ attempted to regenerate it from the crystallized dihydrochloride, but obtained a hydrocarbon which differed decidedly from caryophyllene in its rotatory power.

Occurrence.

The oils in which caryophyllene has been found are by no means so numerous as those from which cadinene dihydrochloride has been obtained. It has been identified by its hydrate in clove, copaiba balsam and canella oils, and by its blue nitrosite in pepper oil. Other oils, judging from the physical properties of the sesquiterpene contained in them, will doubtless be found to contain caryophyllene.

In the following classification the oils are arranged according to

⁴ Ann., 271, p. 285.

⁵ Ann., 279, p. 391.

⁶ Pharm. Archives, 2, p. 280, 298.

⁷ Ann., 271, p. 285.

⁸ Pharm. Archives, 4, p. 164.

the position of the plants in Engler's Syllabus. Four families and four genera, are so far included in this list of plants as yielding caryophyllene.

PIPERACEAE.

Piper nigrum. Black Pepper Oil.

The first analyses of pepper oil, made by Dumas⁹ in 1835, showed it to be almost free from oxygen, the results agreeing with the formula C_5H_8 . Eberhardt¹⁰ in 1887 verified these results. He separated a fraction boiling between 190—250° and a higher one between 250—310°. Both fractions gave results agreeing with the formula $C_{15}H_{24}$. The fraction 190—250° had the specific gravity 0.9042 and a specific rotation of —7°. No chemical work was done on this fraction. Later, this sesquiterpene is reported as cadinene,¹¹ but Schreiner and Kremers,¹² suspecting caryophyllene, rather than cadinene from the physical properties of the fraction obtained by Eberhardt, made a test for this hydrocarbon. They obtained a fraction 125—130° (16 mm.) which had a specific gravity of 0.9058 and showed a rotation of —7.54° and an index of refraction 1.49787. These constants agree fairly well with those of impure caryophyllene. That this hydrocarbon was really under consideration was shown by the preparation of the characteristic blue nitrosite of caryophyllene, melting at 113°.

LEGUMINOSAE.

Copaifera officinalis and other species. Oil of Copaiba.

Blanchet¹³ in 1833 distilled copaiba balsam with water and also by itself. The oil obtained by distillation with water had a sp. gr. of 0.8784 at 22° and boiled at 245°. Analyses indicate the composition C_5H_8 . The oil obtained by direct distillation boiled at 250°, otherwise it had the same properties as the oil distilled with water vapor. With hydrochloric acid it yielded a hydrochloride, which, when dissolved in ether and precipitated with alcohol, melted at 54° and boiled at 185°. Blanchet determined the formula to be $C_{10}H_{16} 2HCl$. Soubeiran and Capitaine¹⁴ in 1840 found the boiling point to be 260° and the specific gravity 0.885; the rotation of the oil was toward the left, somewhat less than French turpentine. With hydro-

⁹ Ann., 1, p. 159; comp. also, Soubeiran and Capitaine, Ann., 84, p. 326.

¹⁰ Arch. d. Pharm., 225, p. 515.

¹¹ Ber. v. S. & Co., Oct. 1898, Suppl. p. 88; Heusler, Die Terpene, p. 175.

¹² Pharm. Archives, 4, p. 61; Proc. Amer. Pharm. Assoc., 49, p. 350.

¹³ Ann., 7, p. 156.

¹⁴ Ann., 84, p. 321.

chloric acid it yielded a hydrochloride called by them copaiba camphor, after the nomenclature then in use. This hydrochloride formed short rectangular prisms, odorless and transparent, melting at 77°. It was decomposed by heat, and on boiling with alcohol an oil was generated. They attempted to regenerate the hydrocarbon, which they called copaivene by heating the hydrochloride, but the high temperature necessary also destroyed in part the hydrocarbon. Analysis gave the same result as found by Blanchet, namely $C_{10}H_{16}$. $2HCl$.

Posselt¹⁵ in 1849 reports on the oil obtained from para copaiba balsam. It had the formula C_5H_8 ; sp. gr. 0.91 and boiled at 252°. It absorbed hydrochloric acid gas readily, but gave no crystalline hydrochloride. Oxidized by heating with dilute nitric acid it yields, besides volatile acids not investigated, a resin and a crystalline acid, which could not be investigated, as the amount was too small.

Strauss¹⁶ in 1868 obtained from Maracaibo copaiba balsam, by dissolving the resin in dilute sodium hydrate solution with the aid of heat, an oil floating on the surface of the solution. This oil had a specific gravity of 0.921 at 10° and boiled from 250 to 260°. Its composition was C_5H_8 , but a vapor density determination agreed with the formula $C_{20}H_{32}$ (?). Oxidation experiments led to no definite results. Brix¹⁷ in 1882 investigated fraction 250—260° of Maracaibo copaiba balsam oil. This fraction had a specific gravity of 0.892 at 17°, an index of refraction of 1.503 and the molecular formula $C_{20}H_{32}$. It yielded no crystalline hydrochloride and on oxidation with chromic acid mixture, acetic and a small amount of terephthalic acid resulted. By treatment with metallic sodium, he obtained in the last portions of the distillate a dark blue oil, corresponding with the improbable formula $3(C_{20}H_{32}) + H_2O$, and called by him "Copaibaöl-Hydrat." Phosphoric acid anhydride changes this again to the original sesquiterpene.

Grünling¹⁸ oxidized the hydrocarbon of copaiba oil boiling at 252° with chromic acid mixture and obtained a crystalline acid, melting at 207°, an indifferent body, melting at 218°, and a small amount of a second acid, melting at 170°. Paracopaiba balsam oil boiling at 258° yielded oxidation products which differed from the above. This oil gave on oxidation an acid melting at 136°.

¹⁵ Ann., 69, p. 67.

¹⁶ Ann., 148, p. 148.

¹⁷ Monatsh. f. Chem., 2, p. 507; Jahrest. d. Pharm., 1881—82, p. 214.

¹⁸ Dissertation, Strassburg, 1879, p. 24.

Levy and Engländer¹⁹ obtained from copaiba oil a fraction 252–256°, which had the composition C₅H₈, and a vapor density agreeing with C₂₀H₃₂, a specific gravity of 0.8978 at 24° and a rotation of –7°. On oxidation with chromic acid mixture they obtained besides acetic acid an amorphous acid, the barium salt of which indicated the formula C₁₂H₁₈O₆, and a well crystallized acid, melting at 140°, which was identified as a symmetric dimethyl succinic acid, C₆H₁₀O₄. The amount of this acid was small, being only 1.5 p. c. of the oil used, and it is, therefore, doubtful whether this acid resulted from the hydrocarbon, or from some other unknown compound accompanying it.

Wallach²⁰ in 1892 identified the sesquiterpene of fraction 250–270° from copaiba oil as caryophyllene by preparing the characteristic hydrate and nitrosochloride of this hydrocarbon.

Umney²¹ in 1893 examined African copaiba oil, which differs in its physical properties from the other varieties. He failed to get a crystalline hydrate or hydrochloride from fraction 264°. By fractionation over metallic sodium he obtained a blue oil similar to that obtained by Brix from the Maracaibo variety.

From the foregoing presentation of the work done on the various copaiba balsam oils, it will be apparent that the reactions given by the different observers are somewhat contradictory, and show that caryophyllene may not be the only sesquiterpene present in the oil and may even be entirely absent in some of the oils, as for instance, in the African copaiba oil examined by Umney. (See also under the section on history and general discussion.)

CANELLACEAE.

Canella alba. Oil of Canella.

Williams²² in 1894 was able to prepare caryophyllene hydrate, melting at 92–95° from fraction 250–255° of canella oil by the method employed by Wallach for making caryophyllene hydrate.

MYRTACEAE.

Eugenia caryophyllata. Oil of Cloves.

In 1836 Ettling²³ obtained from oil of cloves by treating with alkali and distilling with steam, a colorless, highly refractive liquid, having the specific gravity 0.918 at 8°. According to Ettling the composition is C₅H₈ and the boiling point 142–143°.²⁴ The oil absorbed hydrochloric acid gas in large quantity but yielded no crystalline derivative.

¹⁹ Ann., 242, p. 189.

²⁰ Ann., 271, p. 294.

²¹ Pharm. Journ., 53, p. 215.

²² Pharm. Rundschau, 12, p. 184.

²³ Ann., 9, p. 68.

²⁴ A typographical error is probably responsible for this extremely low boiling point. Church, however, also mentions that the hydrocarbon distills at first mainly between 160–165°, and that the higher boiling point is reached only after several distillations. On account of this low boiling point Dumas [Ann., 27, p. 151] expressed the opinion that this hydrocarbon, C₅H₈, was probably identical with turpentine. It may be that the presence of a small amount of water in the oil was responsible for the depression of the boiling point.

Böckmann²⁵ in 1838 also mentions the hydrocarbon which separates on adding some water to a solution of oil of cloves in alkali and heating. Brüning²⁶ in 1857 separated the hydrocarbon in a manner similar to that used by Ettling but finds the boiling point to be 255°. Williams²⁷ in 1858 determined the boiling point at 251° and the specific gravity at 14° was 0.9016. Williams points out that it cannot be an isomer of turpentine oil and that it closely resembles copaiba and cubeb oil, thus recognizing the sesquiterpene nature of the hydrocarbon.

Church²⁸ in 1875 separated the hydrocarbon from clove oil and states that during the first distillation the oil came over below 165°,²⁹ the greater part distilling between 160 and 164°. The boiling point of this was raised to 215–221° by a second distillation and had a specific gravity of 0.9064 at 15°. After treatment with metallic sodium the hydrocarbon boiled at 247° (253.9° corr.) and had a specific gravity of 0.905 at 15°, instead of 0.9064 as before. Analysis and vapor density determination indicated the formula C₁₅H₂₄.

In 1892 Wallach and Walker³⁰ characterized the hydrocarbon from clove oil and gave it the name of caryophyllene, after the genus name of the plant yielding the oil.

Eugenia caryophyllata. Oil of Clove Stems.

Erdmann³¹ in 1897 obtained from the oil of clove stems, by shaking out the eugenol with aqueous potash, a sesquiterpene boiling between 123–125° (18–14 mm.) and having a specific gravity 0.9050. While these properties agree with caryophyllene, nevertheless, in the absence of more definite information concerning this sesquiterpene, it cannot be definitely stated that it is caryophyllene, although it is mentioned as such in several places.

Preparation.

Caryophyllene has been obtained in a fairly pure state from oil of cloves. All the earlier investigators had the impure hydrocarbon which separated from the alkaline solution of clove oil, in hand, but the later workers still further purified this product by distillation and by chemical treatment. All attempts to obtain it in an absolutely

²⁵ Ann., 27, p. 155.

²⁶ Ann., 104, p. 202.

²⁷ Ann., 107, 242.

²⁸ Journ. Chem. Soc., (2) 18, p. 118.

²⁹ This low boiling point may have been due to moisture in the oil.

³⁰ Ann., 271, p. 298.

³¹ Journ. f. prakt. Chem., (2) 56, p. 144.

pure form by regeneration from its derivatives as had been done with cadinene have so far failed; Wallach obtained the isomeric clovène from the hydrate, and Schreiner and Kremers obtained from the dihydrochloride a hydrocarbon which differed decidedly in its rotatory power from caryophyllene.

Wallach³² in 1892 prepared caryophyllene by fractional distillation of the non-eugenol constituents of clove oil. He took the fraction distilling between 258–260°. In 1897 Erdmann³³ showed that the hydrocarbon thus prepared still contained some eugenol in the form of its acetic ester. He recommended saponification with alcoholic potassa and then treating the solution with water to separate the hydrocarbon. By distilling this hydrocarbon under diminished pressure he obtained caryophyllene boiling at 123–124° (13 mm.), 258–259° (752 mm.), which was free from oxygenated constituents.

The caryophyllene used by Schreiner and Kremers³⁴ was prepared on a somewhat larger scale in the laboratory of Fritzsche Bros. at Garfield as follows:

Oil of cloves was treated in slight excess with a 7 p. c. soda solution at ordinary temperature and the solution extracted with ether. The ether invariably dissolved some of the sodium eugenol. The ethereal solution is evaporated on a water bath, at which temperature any of the acetoeugenol originally present in the oil of cloves and dissolved by the ether, is saponified by the sodium present. The crude caryophyllene thus obtained was then thoroughly exhausted of any eugenol by repeated treatment with 5 p. c. soda solution and then rectified by distillation with steam. This product was found to be free from acetoeugenol. When distilled under 20 mm. pressure nearly all of this oil came over between 136–137°.

Physical Properties.

Caryophyllene is a colorless, highly refractive liquid, having when pure, a faint but pleasant odor of aromatic woods, without, however, definitely suggesting any particular variety. Its physical constants as found by various investigators is given in the following tabulation, the arrangement being chronological, giving at the same time the order of purity. All these samples were prepared from oil of cloves.

³² Ann., 271, p. 298.

³³ Journ. f. prakt. Chem., (2) 56, p. 146.

³⁴ Pharm. Archives, 2, p. 278.

Williams (1858): B. p. 251°; $d_{14}^{\circ}=0.9016$.

Church (1875): B. p. 253.9° (corr.); $d_{15} = 0.905$.

Wallach (1892): B. p. 258–260°; $d_{15}^{\circ}=0.9085$. $n_D=1.50094$; optically active.

Erdmann (1897): B. p. 123–124° (13 mm.), 258–259° (752 mm.); $d_{24}^{\circ}=0.9038$.

Schreiner and James (1898): $d_{20} = 0.9032$: $n_D = 1.50019$;
 $[a]_D = -8.74^\circ$.

Schreiner and Kremers (1899); B. p. 136—137° (20mm.); $d_{20}^{\circ} = 0.9030$; $n_p = 1.49976$; $[n]_D = -8.96$.

Schreiner and Kremers also determined the indices of refraction for the three hydrogen lines, the dispersion between the lines being also given.

H _a	1.49694	.01136	.01834
H _β	1.50830		
H _r	1.51528		

The molecular refraction agrees with two double bonds.

Only caryophyllene obtained from clove oil has been considered in the above list, because even moderately pure samples of this hydrocarbon have not been prepared from the other oils, and also because of the contradictory statements found for the hydrocarbons of copaiba oil, which was discussed in the historical part and under copaiba oil in the section on occurrence.

Chemical Properties and Derivatives.

Caryophyllene yields with hydrochloric acid a crystalline dihydrochloride, which is quite stable. Upon hydration it gives a monohydrate, which appears to be a saturated compound. It also gives a nitrosochloride, a nitrosate and a nitrosite. These nitroso-compounds and also the hydrate yield a number of other derivatives. It takes up four atoms of bromine but no crystalline bromide has been obtained.

For the identification of caryophyllene, the preparation of the hydrate has been mostly used. The preparation of the hydrate requires, however, quite a large amount of the sesquiterpene in a fairly pure condition, and even then it may happen that the hydrate is

not obtained in a crystalline form. A more positive test is the preparation of the blue nitrosite as described below, for which only a cubic centimeter or two of the sesquiterpene fraction will be required. The nitrosite is much more readily purified than the hydrate and has a sharp melting point as well as other characteristic properties. In point of time the nitrosite has a decided advantage over the hydrate as a test for identification. For further characterization the hydrate can be changed to its phenyl urethane derivative, and the blue nitrosite into the nitrobenzylamine base, or by light, into the β -compound mentioned below.

The oxidation experiments have nearly all been made on copaiba oil and due to the uncertain purity of the material subjected to oxidation, no definite conclusion can be reached. These results have already been given under copaiba oil in the section on occurrence and need not be repeated here. It may be mentioned that Beckett and Wright,³⁵ by treating caryophyllene from clove oil with dilute nitric acid, obtained neither toluic nor terephthalic acid. Attempts to get cymene by treatment with bromine likewise failed.

Caryophyllene dihydrochloride, C₁₅H₂₄.2HCl.

Wallach³⁶ in 1892 reports that caryophyllene from oil of cloves is capable of adding hydrochloric acid, but that the resulting compound is liquid. In 1899 Schreiner and Kremers³⁷ succeeded in getting this dihydrochloride in a crystalline condition. Blanchet³⁸ as early as 1833 and also Soubeiran and Capitaine³⁹ in 1840, obtained from copaiba balsam oil, later shown by Wallach to contain caryophyllene, a solid hydrochloride, but it would be unsafe to draw the conclusion that these hydrochlorides, melting at 54 and 74°, and the analyses of which agreed with the formula C₁₀H₁₆.2HCl, were identical with caryophyllene dihydrochloride, C₁₅H₂₄.2HCl melting at 69–70°.

Schreiner and Kremers⁴⁰ prepared the dihydrochloride as follows: Caryophyllene is dissolved in an equal volume of ether and the solution saturated with hydrochloric acid gas at 0°. After standing for about 24 hours the ether is allowed to evaporate and the heavy viscous oil mixed with alcohol, in which it is but very sparingly soluble when cold, and this mixture exposed to a low temperature.

³⁵ Journ. Chem. Soc., (8) 1, p. 6.

³⁶ Ann., 271, p. 298.

³⁷ Pharm. Arch., 2, p. 296; Proc. Amer. Pharm. Assoc., 47, p. 178.

³⁸ Ann., 7, p. 154.

³⁹ Journ. de Pharm., 26, p. 65.

⁴⁰ Pharm. Arch., 2, p. 296.

The undissolved lower layer of liquid dihydrochloride will soon solidify and form a solid mass of crystals. These may then be pressed on a porous plate to free them from any adhering oily matter and recrystallized from a little hot alcohol. This should be done quickly, a small quantity at a time, as continued boiling with alcohol decomposes the dihydrochloride.

The recrystallized product occurs in fine white needles, melting at 69–70°.

The dihydrochloride when treated with glacial acetic acid and anhydrous sodium acetate, yields a hydrocarbon which does not appear to be identical with caryophyllene nor with clovane obtained by Wallach from the hydrate of caryophyllene. Whether the regenerated oil is an individual compound has not been determined, but the indications are that isomerization of the caryophyllene has taken place.

Caryophyllene nitrosochloride, $C_{15}H_{24}NOCl$.

Wallach⁴¹ in 1892 prepared some of the nitrosochloride, but complains of the exceedingly small yield. Schreiner and Kremers⁴² in 1898 found that the action of light had much to do with the formation of the insoluble white bisnitroso compound from the soluble blue compound. They prepared the nitrosochloride as follows: 5 cc. of caryophyllene, 5 cc. of alcohol, 5 cc. of ethyl acetate and 5 cc. of ethyl nitrite are mixed and well cooled in a freezing mixture. 5 cc. of a saturated solution of hydrochloric acid gas in cold alcohol are then slowly added, continually rotating the flask. After allowing the solution to stand for about an hour in the cold, it is exposed to the light. The blue color soon fades away and the nitrosochloride begins to separate. The complete separation requires several days or even weeks, during which time the solution is best kept cold, although it may be allowed to warm up without any serious effect, as the nitrosochloride is fairly stable, even while in contact with the mother liquor. The nitrosochloride is collected and washed with alcohol.

The nitrosochloride thus obtained is a white stable compound and melts at 158° with decomposition. Wallach found the melting point to be 161–163°.

According to Schreiner and Kremers the nitrosochloride yields a mixture of two nitrol benzylamine bases which can be separated by

⁴¹ Ann., 271, p. 295.

⁴² Pharm. Arch., 2, p. 298.

crystallization. They melt at 128° and 167° respectively. This may indicate that the nitrosochloride consisted of a mixture of two isomers.

The reaction with aniline has not been fully studied. One sample of freshly prepared nitrosochloride gave an energetic reaction when heated with aniline and alcohol the solution becoming of a deep purple color, which may have been due to the formation of amidoazo benzene as noticed by Wallach⁴³ in the regeneration of pinene from its nitrosochloride by aniline. No nitrol aniline base of caryophyllene could be obtained from the product of the reaction. A second sample of nitrosochloride, which had been prepared a year previous, when similarly treated, reacted much less violently, the product of the reaction being less deep in color, and yielding a nicely crystallized derivative.⁴⁴ From this it would appear that under certain conditions a nitrol aniline base can be obtained and under other conditions a splitting off of the nitrosylchloride takes place with regeneration of a hydrocarbon. Perhaps this behavior of the nitrosochloride is due to varying proportions of the two possible modifications mentioned above. Further study is necessary to decide these points and if found to be true, it would be of great interest to prepare some of the generated hydrocarbon and study its properties.

A molecular weight determination shows the nitrosochloride to belong to the class of bis-nitroso compounds.

Caryophyllene nitrosate, C₁₅H₂₄N₂O₄.

Wallach and Tuttle⁴⁵ in 1894 prepared the nitrosate as follows: 10 cc. of the caryophyllene fraction of clove oil, 9 cc. of amyl nitrite and 16 cc. of glacial acetic acid are cooled to -15° in a freezing mixture and a similarly cooled mixture of glacial acetic acid and conc. nitric acid is slowly added with constant agitation. The solution becomes green and a white crystalline precipitate separates. As soon as the mixture becomes dark green, some alcohol is added, and after standing for about two hours, the separated nitrosate is collected on a filter.

Schreiner and Kremers⁴⁶ proceeded as follows: 5 cc. of caryophyllene, 5 cc. of glacial acetic acid and 5 cc. of ethyl nitrite, are mixed and well cooled in a freezing mixture. A mixture of 5 cc. of conc. nitric acid and 5 cc. of glacial acetic acid is then slowly added, continually rotating the flask. At the end of the reaction alcohol

⁴³ Ann., 252, p. 182; 158, p. 848.

⁴⁴ Unpublished result.

⁴⁵ Ann., 279, p. 891.

⁴⁶ Pharm. Arch., 2, p. 296; Proc. Amer. Pharm. Assoc., 47, p. 178.

is added and after about two hours, the separated nitrosate is collected on a force filter, washed with cold alcohol and dried on a porous plate.

The nitrosate is insoluble in alcohol, ether, glacial acetic acid, but soluble in benzol, from which it crystallizes in fine transparent needles, melting at 148–149° with decomposition.

Wallach prepared from it a nitrol piperidine base, melting at 141–143°. Schreiner and Kremers obtained a nitrol benzylamine base melting at 128°, identical with the lower melting nitrolbenzylamine base obtained from the nitrosochloride.

Molecular weight determinations show the nitrosate to be a bis-nitroso compound.

Caryophyllene nitrosite, $C_{15}H_{24}N_2O_3$. According to Schreiner and Kremers⁴⁷ this is prepared as follows: Equal parts of caryophyllene, low boiling petroleum ether, a saturated solution of sodium nitrite and lastly glacial acetic acid, are mixed, continually agitating the solution. On adding the acid, the upper petroleum ether layer is colored a beautiful blue, which becomes darker as more acid is added. This solution is allowed to stand a few minutes and is then strongly cooled in ice water or a freezing mixture. Upon standing, or better upon agitation, the upper blue layer solidifies to a mass of deep blue crystals. Crystallization usually takes place when so treated, but should it fail, the merest trace of solid nitrosite brought in contact with the cold solution will cause it to solidify immediately to a mass of crystals. The magma is transferred to a force filter, first washed with cold alcohol, then with water, and lastly with a little more cold alcohol, in which the nitrosite is but sparingly soluble. The yield obtained is from 12 to 14 p. c. Throughout this work the solutions must not be exposed to bright light as the blue compound is decomposed by such treatment.

The nitrosite can be recrystallized from hot alcohol in the dark, in which it is very soluble, but which deposits the nitrosite in beautiful deep blue needles on cooling. The melting point of the purified product is 113°. It is perfectly stable up to its melting point, but when this is reached a gas is given off and the liquid becomes green and finally brown. The nitrosite is dextrorotatory, $[\alpha]_D = +102.95^\circ$ in a benzol solution. Molecular weight determinations show it to be monomolecular, nor does it react with benzoyl

⁴⁷ Pharm. Arch., 2, p. 278.

chloride. These facts indicate that in the blue nitrosite there is present a true nitroso group.

The nitrosite yields a nitrolbenzylamine base melting at 167°, which is identical in its properties with the higher melting nitrolbenzylamine base obtained from the nitrosochloride, but different from that obtained from the nitrosate.

This blue nitrosite is very suitable for the identification of caryophyllene in volatile oils. It can be prepared readily from fractions of the proper boiling point and is in every respect a characteristic compound which can be readily purified. Only a very small amount of material is necessary for this test, the caryophyllene in pepper oil having been identified with 2 cc. of the fraction of proper boiling point. For further characterization the β -compound mentioned below or the nitrolbenzylamine derivative can be prepared from it.

The nitrosite is exceedingly stable in the dry form, but when exposed to light in a dissolved condition it readily decomposes in part and suffers molecular changes. This reaction takes place in the red end of the spectrum only and differs somewhat according to the solvent used. The two following compounds have been obtained by Schreiner and Kremers as the result of the action of light on the nitrosite.

α -Compound. This was prepared as follows: 5 gr. of caryophyllene nitrosite were mixed with 20 cc. of absolute alcohol and exposed to sunlight. The blue crystals gradually dissolved in the alcohol to form a colorless, or only slightly yellowish solution. Oxides of nitrogen appear to be given off at the same time, although this could not be definitely determined. On spontaneous evaporation an oil remained from which crystals separated in the form of radiating needles. The yield of this product is small, amounting to only 5 p. c. of the nitrosite used.

This compound occurs in transparent, well developed crystals, melting at 113–114°. It is readily soluble in alcohol and benzol, differing in this respect from the β -compound described below. A nitrogen determination agrees with the formula $C_{15}H_{24}N_2O_3$ and it would, therefore, appear to be an isomer of the blue nitrosite, although this is by no means certain as only a nitrogen determination could be made with the small amount of material at hand. It is monomolecular.

β -Compound. This is obtained by exposing a benzol solution of the nitrosite to sunlight. The blue nitrosite is very soluble in benzol and when this solution is exposed to sunlight, nitrogen gas is given off and the blue solution decolorizes, and solidifies to a mass of fine white felt-like crystals. The yield was about 12 p. c. of the blue nitrosite used.

The substance thus obtained was pure white and showed a matted felt-like mass of crystals under the microscope. It differs in all its properties from those of the α -compound described above. The melting point of the α -compound is 113—114°; that of the β -compound 146—148°. The crystals are decidedly different in appearance. The α -compound is readily soluble in both alcohol and benzol, whereas the β -compound is insoluble in these solvents. It is also insoluble or only sparingly soluble in ether, chloroform and carbon disulphide. It is soluble in boiling ethyl acetate, but cannot be recovered in a crystalline condition.

This β -compound reacts readily with benzoyl chloride and also with benzylamine, but no crystalline compounds have so far been obtained.

The exact nature of this as well as the α -compound can only be decided by further study.

Caryophyllene nitrobenzylamines, $C_{15}H_{24}(NO)NHCH_2-C_6H_5$. There appear to be two nitrobenzylamines, which differ from each other in crystal form and melting point. According to Schreiner and Kremers⁴⁸ caryophyllene nitrosite yields a-nitrobenzylamine base melting at 167° and the nitrosoate a base melting at 128°, while the nitrosochloride yields both these bases. For the present these bases have been designated as α - and β -nitrobenzylamine respectively.

α -Nitrobenzylamine. This compound was obtained as follows: Nitrosite and benzylamine were heated together in alcoholic solution for a short time. The crystals which separated on cooling were well washed with water and recrystallized from hot alcohol. The base separates on cooling in pure white needles, melting at 167°. This nitroamine base obtained from the nitrosite was identical with the first crop obtained from the nitrosochloride as follows: The product obtained by heating together nitrosochloride and benzylamine was heated with alcohol and set aside to crystallize. On cooling a mass of fine needle-shaped crystals separated. These were

⁴⁸ Pharm. Arch., 2, p. 285.

collected, washed with alcohol and then with water, to separate any salts of benzylamine. The washed product was then recrystallized from alcohol, from which it separated on cooling in pure white needles of the melting point 167°.

On standing, the mother liquor from the crude base deposited crystals of the β -nitrolamine described below.

β -Nitrobenzylamine. This was obtained as follows: Caryophyllene nitrosate was boiled with benzylamine and alcohol until completely dissolved. The alcoholic solution deposited on standing, nodules of crystals on the sides and bottom of the dish. These, when recrystallized from alcohol, again separated in nodules, and showed a melting point of 128°. This nitrolamine-base is identical with the nitrolamine obtained from the mother liquor of the α -nitrolamine prepared from the nitrosochloride as mentioned above.

Caryophyllene nitropiperidine, $C_{15}H_{24}(NO)NHC_5H_{10}$. Wallach and Tuttle⁴⁹ prepared this compound by treating the nitrosoate with piperidine. Recrystallized from alcohol it forms transparent needles melting at 141—143°.

Caryophyllene hydrate, $C_{15}H_{25}OH$. Wallach and Walker⁵⁰ employed the hydration method of Bertram for the preparation of this compound. To a mixture of 1000 gr. of glacial acetic acid, 20 gr. of conc. sulphuric acid and 40 gr. of water, 25 gr., or as much as will dissolve, of caryophyllene are added, and the solution heated for about 12 hours in a waterbath. The product of the reaction is distilled with steam. Acetic acid and oil pass over first, followed by a less volatile oil, which soon solidifies to a crystalline mass. To free it from adhering oily matter, the mass is strongly cooled and pressed on porous plates. When dry it is best purified by direct distillation from a wide necked retort and subsequent crystallization from alcohol, which raises the melting point from 94—95° to 96°.

The hydrate boils constant without apparent decomposition at 287—289°. By applying heat slowly it can be sublimed in fine glistening needles. It is almost insoluble in cold water, slightly soluble in hot. It is very soluble in ether, alcohol, benzol, ligroin, and carbon disulphide. By slow crystallization from alcohol it forms well developed, hexagonal, rhombic hemihedral crystals. The solid compound is almost odorless, but the vapors have a weak but pleasant odor, reminding of pine needles.

⁴⁹ Ann., 279, p. 892.

⁵⁰ Ann., 271, p. 288.

The hydrate is optically inactive and is a saturated compound. All of its derivatives are likewise saturated. Caryophyllene is, however, a hydrocarbon with two double bonds, as is shown by its molecular refraction and formation of a dihydrochloride. It appears, therefore, that the hydration process has changed the caryophyllene into an isomeric sesquiterpene. This is also borne out by the fact that caryophyllene cannot be regenerated from the hydrate. Dehydration agents give rise to an isomer, which has been called clovène (see this). On the other hand, the hydrate is not a derivative of clovène, because this hydrocarbon cannot be changed back into the hydrate from which it was generated. It seems therefore that the hydrate, while obtained from caryophyllene, is not a true derivative of it, but of another isomeric sesquiterpene, having only one double bond, but which does not appear to be clovène.

The hydrate also yields a chloride, bromide, iodide, acetate, and nitrate, none of which have so far been prepared from caryophyllene direct and appear to be derivatives of the sesquiterpene which forms the base of the hydrate, as they are all saturated and optically inactive compounds.

Chloride, $C_{15}H_{25}Cl$. Molecular amounts of the hydrate and phosphorus pentachloride are mixed in a flask from which moist air is excluded.⁵¹ After a time the mass heats up and becomes liquid, while hydrochloric acid gas escapes. The phosphorus oxychloride formed is distilled off in a vacuum and the residue, washed with water and dilute soda solution, solidifies when cooled. Recrystallized from alcohol the pure chloride melts at 63° and distills without decomposition at $293-294^\circ$. It can also be recrystallized from ethyl acetate or ligroin. The chloride is very stable; it does not even lose its chlorine by boiling for a short time with aniline. It is optically inactive.

Bromide, $C_{15}H_{25}Br$. Wallach⁵² prepares this as follows: 10 gr. of the hydrate are warmed with a slight excess of phosphorus tribromide. Hydrobromic acid is given off. The product of the reaction is washed with cold water and a little ammonia. The oil, which at first separates soon solidifies to a crystalline mass. Recrystallized from alcohol it forms rhombic crystals melting at $61-62^\circ$.

The bromide may also be prepared as follows: To a solution of

⁵¹ Wallach, Ann., 271, p. 289.

⁵² Wallach, Ann., 271, p. 290.

yellow phosphorus in carbon disulphide, add for each atom of phosphorus three atoms of bromine and lastly one molecule of the hydrate. The carbon disulphide is removed by distillation and the residue washed and treated as mentioned above. It is optically inactive.

Iodide, $C_{15}H_{25}I$. This is prepared by Wallach⁵³ in a manner similar to that just described for the bromide. To 1 gr. of phosphorus dissolved in carbon disulphide add the calculated amount of iodine to form PI_3 and lastly 15 gr. of the hydrate. The carbon disulphide is distilled off and the residue treated as with the bromide.

The iodide crystallizes in long white needles or rhombic prisms, melting at 61° . It is decomposed by heat and is optically inactive.

When this iodide is treated in ethereal solution with metallic sodium, a hydrocarbon $C_{30}H_{50}$ results. By several crystallizations from ethyl acetate, and lastly from absolute alcohol, Wallach and Tuttle⁵⁴ obtained this compound in large transparent, well developed prisms, melting at $144-145^\circ$. This hydrocarbon is saturated and is not attacked by oxidizing agents, behaving in this respect like the paraffins.

Acetate, $C_{15}H_{25}O.COCH_3$. This compound is prepared by Wallach and Tuttle by digesting the iodide with sodium acetate and glacial acetic acid for several hours. The product of the reaction is distilled with steam, washed with dilute alkali to separate any iodine, and dried. On distilling it solidifies partially, and is purified by expression and recrystallization from methyl alcohol. No melting point is given.

Nitrate, $C_{15}H_{25}O.NO_2$. Wallach and Walker⁵⁵ prepare this ester as follows: Caryophyllene hydrate is liquified by a small amount of alcohol and strongly cooled. Fuming nitric acid is then added drop by drop with constant agitation until a strong excess of the acid is present. After several hours standing at room temperature, the nitric acid ester crystallizes out in fine, colorless needles. These are filtered off and on adding some water to the filtrate more of the ester separates, although somewhat sticky. This impure portion is readily purified by distillation with steam.

The nitrate is soluble in alcohol, ether and benzol, but much less so in alcohol than the original hydrate. It crystallizes in color-

⁵³ Ann., 271, p. 290.

⁵⁴ Ann., 279, p. 398.

⁵⁵ Ann., 271, p. 291.

less rhombic prisms melting at 96°. The ester is saponifiable only with difficulty and is optically inactive.

Urethane, $C_{15}H_{25}O.CO.NHC_6H_5$. Wallach and Tuttle⁵⁶ prepared this by warming together in a water-bath molecular quantities of caryophyllene hydrate and carbanil. The urethane is separated from the diphenyl urea formed at the same time by crystallization from ether-alcohol. It crystallizes in needles melting at 136–137°.

8. Cedrenes.

The word cedrene was first applied by Walter⁵⁷ in 1841 to the hydrocarbon generated from cedar camphor (cedrol). Beckett and Wright⁵⁸ in 1876 and Gladstone⁵⁹ in 1887 applied the name cedrene to all members of the $C_{15}H_{24}$ group, which accounts for the designation cedrene being used by Muir⁶⁰ for the sesquiterpene of sage oil (see this) the properties of which are quite different from the cedrene of cedarwood oil. Chapman and Burgess,⁶¹ Rousset⁶² and others apply the name to the hydrocarbon found naturally in the oil. Walter claims that these two hydrocarbons are identical. The same view is expressed by Gildemeister and Hoffmann,⁶³ but until further evidence is forthcoming they must be considered as distinct sesquiterpenes. In the following the two hydrocarbons will be respectively referred to under the names, natural cedrene and cedrene from cedrol.

History and General Discussion.

Walter⁶⁴ in 1841 found that when cedar-wood oil was distilled, it boiled within 273 and 282° and that the distillate solidified to a mass of crystals. Separating these and recrystallizing them from alcohol, he obtained the compound in a purer form. From this compound he obtained, by treatment with phosphoric acid anhydride, a hydrocarbon which he called cedrene. Walter also obtained a hydrocarbon directly from the oil. This he considers as identical with cedrene from cedrol. Walter gave to the crystalline compound (cedrol) the formula $C_{16}H_{24}+H_2O$ and to cedrene the formula $C_{16}H_{24}$. In the second article Walter⁶⁵ gives the composition as $C_{16}H_{28}O$ and

⁵⁶ Ann., 279, p. 392.

⁵⁷ Ann., 39, p. 247.

⁵⁸ Journ. Chem. Soc., (8), 1, p. 6.

⁵⁹ Chem. News, 54, p. 828.

⁶⁰ Pharm. Journ., 37, p. 994; Journ. Chem. Soc., 37, p. 678.

⁶¹ Proc. Chem. Soc., No. 168, p. 140; Chem. News, 74, p. 95.

⁶² Bull. Soc. Chim., (3), 17, p. 485.

⁶³ Die Aeth. Oele, p. 357.

⁶⁴ Ann., 39, p. 247.

⁶⁵ Ann., 48, p. 385.

$C_{16}H_{26}$ respectively. He also states that the natural cedrene, when repeatedly distilled from potassium has the same properties as the cedrene prepared from the crystalline body (cedrol).

Gladstone⁶⁶ in 1871 determined the physical properties of cedrene obtained by the distillation of cedarwood oil with phosphoric acid anhydride. Chapman and Burgess in 1896 and Heine and Co.⁶⁷ distilled cedrene directly from the oil and determined its physical properties. Rousset in 1897 isolated cedrene and also the crystalline body, which he calls cedrol, from the oil. He showed that cedrene was a sesquiterpene and cedrol a sesquiterpene hydrate. Rousset also studied these compounds chemically; from cedrene he prepared a ketone, cedrone, by oxidation, and by reducing this, an alcohol, isocedrol.

Preparation.

Natural cedrene. This is prepared by separating it from the cedrol in oil of cedarwood by distillation, preferably in a vacuum. Since cedrol is not always present in the oil, the preparation is at times very simple. The boiling point of the hydrocarbon is lower than that of cedrol.

Walter⁶⁸ prepared the hydrocarbon by repeatedly distilling the liquid portions from which he had separated the cedrol, collecting the fraction 264—268° and then rectifying this by several distillations from metallic potassium.

Chapman and Burgess prepared cedrene by distillation under diminished pressure and Rousset collected fraction 125—130° under a pressure of 9 mm. This fraction was further purified by rectification from sodium.

Cedrene from cedrol. Walter⁶⁹ prepared a hydrocarbon, which he called cedrene from the crystallized portion of cedarwood oil by treatment with phosphoric acid anhydride. The anhydride was added in small portions to the molten crystals and the cedrene distilled off. This operation was repeated several times. Walter⁷⁰ found that it could be further purified by distillation from metallic potassium, until the metal is no longer attacked. This latter treatment lowers the boiling point by more than ten degrees.

⁶⁶ Journ. Chem. Soc., (2), 10, p. 5; Pharm. Journ., 81, p. 705.

⁶⁷ List of products exhibited at Paris 1900.

⁶⁸ Ann., 39, p. 251; 48, p. 38.

⁶⁹ Ann., 39, p. 249.

⁷⁰ Ann., 48, p. 86.

Rousset⁷¹ also obtained this sesquiterpene by dehydration of cedrol. It also resulted together with an acetate when cedrol was heated to 100° in sealed tubes with acetic acid anhydride, and on oxidizing cedrol with chromic acid in acetic acid solution.

Schimmel & Co. prepared cedrene by the action of formic acid without the application of heat.

Physical Properties.

Natural cedrene is a colorless, somewhat viscid liquid. The properties of natural cedrene as found by various investigators are as follows:

Walter (1841): B. p. 264—268°; $d_{14.5} = 0.98$.

Walter (1843): The same properties as cedrene from cedrol after treatment with metallic potassium.

Chapman and Burgess (1896): B. p. 261—262°; $d_{15} = 0.9359$; $[\alpha]_D = -60^\circ$; $nH\alpha = 1.4991$, $n_D = 1.5015$.

Rousset (1897): B. p. 131—132° (10 mm.); $\alpha_D = -47^\circ 54'$.

Heine & Co. (1900): B. p. 261—262°; $d_{15} = 0.939$; $\alpha_D = -48^\circ$.

Cedrene from cedrol. The properties found for the hydrocarbon prepared from cedrol are as follows:

Walter (1841): B. p. 248°; $d_{14.5} = 0.984$.

Walter (1843): B. p. 287°.

Gladstone (1871): B. p. 252°; $d_{18} = 0.9231$; $n_A = 1.4964$.

Rousset (1897): B. p. 115—117° (6.5 mm.).

Schimmel & Co. (1897): B. p. 262—263°; $\alpha_D = -80^\circ$.

Chemical Properties.

Natural cedrene. Chapman and Burgess state that cedrene readily combines with hydrochloric acid and with bromine, but that no definite compounds could be isolated. Negative results were also obtained in the case of the oxides of nitrogen and nitrosyl chloride. Rousset obtained similar results with bromine and the hydrohalogens. The compounds soon decomposed, giving off hydrohalogen and by distillation in a vacuum the hydrocarbon was again generated.

When cedrene is oxydized with chromic acid in glacial acetic acid a ketone of the formula $C_{15}H_{24}O$ results, which Rousset has called cedrone. This ketone boils at 147—151° (7.5 mm.), does not combine with sodium bisulphite, but yields iodoform, which shows

⁷¹ Bull. Soc. Chim., (8), 17, p. 488.

that the grouping —CO—CH_3 is present or readily formed. With hydroxylamine it yields an oxime boiling at 175—180° (8 mm.), which, heated with glacial acetic acid, gives an acetate of the oxime boiling at 185—190° (9 mm.).

The ketone yields by reduction with sodium an alcohol, called *isocedrol*. It is a very viscous, colorless liquid boiling at 148—151° (7 mm.) and corresponding to the formula $\text{C}_{15}\text{H}_{26}\text{O}$. Rousset prepared from this alcohol its benzoic ester boiling at 221—223° (6 mm.) and having the formula $\text{C}_{15}\text{H}_{25}\text{OCO.C}_6\text{H}_5$.

If the oxidation is more violent than that used for the preparation of the cedrone a very viscous acid, boiling between 220 and 230° under 9 mm. pressure, and having the formula $\text{C}_{12}\text{H}_{18}\text{O}_3$ results. The silver salt of this acid has the composition $\text{C}_{12}\text{H}_{17}\text{O}_3 \text{Ag}$. Another product of the oxidation is dimethyl ketone. Nitric acid produces only resin acids, and alkaline permanganate solution gives no better results. Cedrene cannot be hydrated by the action of water, sulphuric acid and glacial acetic acid. Submitted to destructive distillation under pressure, there result benzene, toluene, napthalene, anthracene and other hydrocarbons.

Cedrene from cedrol. Neither Walter, Gladstone nor Rousset report any chemical work on this sesquiterpene.

Sesquiterpene Hydrate Yielding Cedrene. Cedrol. The alcohol formerly known as cedar camphor, was separated by Walter from the oil of cedarwood by expressing the semisolid distillate and by recrystallization from alcohol it was obtained in white crystals. Rousset isolated it from the oil by fractional distillation under diminished pressure and then purifying the solidified distillate by several recrystallizations from methyl alcohol.

Cedrol is, however, not always a constituent of cedarwood oil. The readiness with which cedrol splits off water with the production of cedrene, has already been mentioned. On oxidation cedrol does not yield an aldehyde or a ketone and may, therefore, be considered as a tertiary alcohol. By treatment with glacial acetic acid or benzoyl chloride no esters are produced, the hydrocarbon being generated.

The physical properties of cedrol are as follows:

Walter (1841): M. p. 74°; b. p. 282°.

Rousset (1897): M. p. 84°; optically active.

9. Clovrene.

When caryophyllene hydrate is treated with dehydrating agents a hydrocarbon is generated which Wallach⁷² has called clovrene after clove oil. It is isomeric with caryophyllene but contains only one double bond whereas caryophyllene contains two.⁷³ It has not been found in nature.

Preparation. According to Wallach and Walker⁷⁴ clovrene is best prepared with the aid of phosphoric acid anhydride as follows: 10 gr. of caryophyllene hydrate are heated almost to the boiling point of the hydrate with an excess of phosphoric acid anhydride for fifteen minutes. After cooling, the hydrocarbon is distilled off with steam and again treated with phosphoric acid anhydride and then rectified by distillation.

Properties. Clovrene has the following properties:

B. p. 261–263°; $d_{18}^{\circ} = 0.930$; $n_b = 1.50066$. The molecular refraction found is 64.77; calculated for $C_{13}H_{24}$ = it is 64.45.

Clovrene has so far not been changed back to the crystalline hydrate, nor has it yielded a crystalline nitrosochloride or other derivative.

10. Comimene.

Stenhouse and Groves⁷⁵ in 1876 obtained from conima resin⁷⁶ an oil which boiled principally between 260–273°. By repeated treatment with sodium and fractionation they obtained a hydrocarbon of the formula $C_{15}H_{34}$ boiling at 264°. The name comimene was given to this sesquiterpene although no chemical work or determination of other physical properties is reported.

11. Cubebene.

The name cubebene was formerly applied to cadinene, which is a principal constituent of cubeb oil. At present the word cubebene is used to designate the hydrocarbon obtained by dehydration from cubeb camphor, a sesquiterpene hydrate found in cubeb oil. Cubeb camphor readily splits off water and yields cubebene, a liquid boiling between 250–260°.⁷⁷ This dehydration takes place so readily that

⁷² Ann., 271, p. 294.

⁷³ For discussion see under caryophyllene hydrate.

⁷⁴ Ann., 271, p. 294.

⁷⁵ A. n., 180, p. 253; Journ. Chem. Soc., 1876 (1), p. 175.

⁷⁶ Bellstein (Vol. III, p. 538) includes leacin, also obtained from elemi resin, in the list of sesquiterpenes by mistake. The composition of leacin is $C_{46}H_{78}O$ (Stenhouse and Groves, Ann., 180, p. 258) or $C_{47}H_{78}O$ (Hesse, Ann., 192, p. 181).

⁷⁷ Ber., 10, p. 189.

the mere keeping of the hydrate over sulphuric acid will cause a partial dehydration. Cubebene has not been prepared in a pure condition, nor has it been studied chemically.

Sesquiterpene hydrate yielding cubebene. Cubeb camphor. The sesquiterpene hydrate, called cubeb camphor, is found in the oil distilled from old cubebs. It is not contained in the oil from fresh cubebs.⁷⁸ It is obtained by exposing the oil to a low temperature, and after separating from the liquid portions of the oil, it is purified by recrystallizing from alcohol.

The compound was probably first observed by Teschemacher early in the nineteenth century. Later, it was investigated by Müller⁷⁹ (1832), Blanchet and Sell⁸⁰ (1833), Winkler⁸¹ (1833), Schmidt (1870 and 1877)⁸² and Schaer and Wyss⁸³ (1875).

Cubeb camphor crystallizes in white, rhombic crystals which smell and taste but slightly after cubebs, having more of a camphoraceous, cooling taste, than the biting taste of cubebs. It is soluble in alcohol, ether, carbon disulphide, chloroform and petroleum ether. It rotates the plane of polarized light to the left.

The physical constants given by various investigators are as follows:

Winkler (1833); M. p. 55—56° R. (68.7—70° C.); b. p. 120—124° R. (150—155° C.)

Schmidt (1870—1877); M. p. 65°; b. p. 148°.

Schaer and Wyss (1875); M. p. 67°; b. p. 148°.

12. Galipene.

The name "galipene" was first applied by Beckurts and Troeger⁸⁴ to the déxtrogyrate hydrocarbon obtained from the alcohol galipol. The derivatives of this "galipene"⁸⁵ were later shown to be cadinene derivatives.⁸⁶ The name of galipene⁸⁷ was then given to the inactive sesquiterpene isolated by fractional distillation and treatment with phosphoric pentoxide from the oil of angostura bark by Beckurts and Troeger. The same inactive sesquiterpene could be obtained from the oil after it had been treated with hydrobromic acid for the

⁷⁸ Arch. d. Pharm., 191, p. 23.

⁷⁹ Ann., 2, p. 90.

⁸⁰ Ann., 6, p. 294.

⁸¹ Ann., 8, p. 208.

⁸² Arch. d. Pharm., 191, p. 28; Ber., 10, p. 188.

⁸³ Arch. d. Pharm., 206, p. 816.

⁸⁴ Arch. d. Pharm., 285, p. 528.

⁸⁵ Arch. d. Pharm., 286, p. 397.

⁸⁶ See under Cadinene.

⁸⁷ Arch. d. Pharm., 286, p. 408.

preparation of the hydrobromide of cadinene. This sesquiterpene boils at 255–260°; $d_{190}=0.912$; $n_D=1.50513$. With hydrochloric acid it forms liquid addition products which decompose readily.

From the method of isolation it does not follow that this inactive sesquiterpene is really contained in the oil. The action of the hydrobromic acid as well as the many distillations under ordinary pressure have doubtless changed the original oil to a considerable extent.⁸⁸ The characterization of this sesquiterpene is too indefinite to justify a specific name.

13 Guajene.

By dehydration of guajol from oil of guaiac wood, Wallach and Tuttle¹ obtained a sesquiterpene, which has not been identified with any of the known sesquiterpenes, but has not been sufficiently studied to be at all characterized as an individual.

Preparation. These chemists prepared the hydrocarbon as follows: 10 gr. of guajol were heated with an excess of zinc chloride to 180° for about an hour. The colored product of the reaction was then distilled with steam. The blue oil obtained was dried with solid caustic alkali and distilled in a vacuum. The fraction boiling at 124–132° (13 mm.) was collected, but analysis showed that the hydrocarbon was not quite pure.

Properties. The fraction thus obtained is blue, but it must not be assumed that this is necessarily due to the hydrocarbon. The production of small amounts of oxygenated compounds from the readily oxidized sesquiterpene are probably responsible for the coloration. According to Wallach and Tuttle this blue color disappears when the hydrocarbon is kept for some time in contact with metallic sodium.

The sesquiterpene has the following physical constants:

B. p. 124–128° (13 mm.); $d_{20}=0.910$; $n_D=1.50114$.

No chemical work is reported.

Sesquiterpene hydrate yielding guajene. Guajol. Schimmel and Co.² obtained as the principal constituent an alcohol from guaiac wood oil. As the latter has erroneously been brought into commerce as champaca wood oil, the alcohol has also been designated as champacol.³ The compound was more closely studied by Wallach and Tuttle⁴ in 1894.

⁸⁸ See under Cadinene.

¹ Continued from Pharm. Archives, vol. 6, p. 141.

¹ Ann., 279, p. 396.

² Ber. v. S. & C., April 1892, p. 42.

³ Merck & Co. Geschäftsbericht, Jan. 1, 1898; Chem. Ztg. Repert., 17, p. 31; Ber. v. S. & Co., April 1898, p. 83; Ann., 279, p. 395.

⁴ Ann., 279, p. 395.

Preparation. Shortly after distillation the viscous guaiac wood oil will solidify completely to a mass of crystals of guajol. Wallach and Tuttle purified the crude alcohol as follows: The crude material was first distilled in a vacuum. The yellowish syrupy portion collected at 155–165° (13 mm.) soon solidified. The crystalline mass was mixed with ether to form a thick paste which was spread on porous plates. By recrystallizing from alcohol the guajol could be obtained in a pure condition. Analysis showed it to be a sesquiterpene hydrate.

Properties. Guajol crystallizes readily in large, well developed, transparent prisms. When pure it shows the following properties:

Schimmel & Co.: M. p. 91°; b. p. 148° (10 mm.) laevogyrate.

Wallach and Tuttle: M. p. 91°; b. p. 288°.

Especially characteristic for guajol are the brilliant color changes which are produced by dehydrating agents. Dilute sulphuric acid, which acts readily on patchouly alcohol, does not act on guajol, but phosphoric pentoxide abstracts water at a high temperature, developing a deep red color, and giving rise to a hydrocarbon and much resinous material. The same reaction takes place, but with better results, when chloride of zinc is employed as has been described above.

According to Schimmel & Co.⁵ guajol yields with acetic acid anhydride a liquid acetic ester, boiling at 155° (10 mm.). Guajol can be regenerated from it by saponification.

14. Gurjunene.

Werner¹ in 1862 examined oil of gurjun balsam and found it to consist principally of a hydrocarbon $C_{20}H_{32}$, boiling at 255°, having a specific gravity of 0.9044 at 15° and a rotation of –10°. Two vapor density determinations made by Kohlrausch² in 1879 show the formula to be that of a sesquiterpene, $C_{15}H_{24}$. According to Flückiger it absorbs hydrochloric acid but yields no crystalline hydrochloride. The chemical work done on this sesquiterpene is restricted almost entirely to color reactions when treated with acids. Flückiger gives the following test for the identification of gurjun balsam oil. The oil when dissolved in about twenty times its weight

⁵ Ber. v. S. & Co., April 1892, p. 42.

¹ Ztsch. f. Chem., 5, p. 588; Jahresh. d. Pharm., 1863, p. 50.

² Flückiger, Pharmacognosie, 3rd ed., p. 102.

of carbon disulphide gives with a drop of a cold mixture of equal parts of sulphuric and nitric acids (1.180) a bright red color which gradually changes to violet.

Although gurjun balsam oil consists almost wholly of sesquiterpenes it is by no means certain that only one sesquiterpene is present. The widely varying rotatory powers of different samples of oil, from $\alpha_D = -35^\circ$ to -130° indicate that the oil may not be a chemical unit. In one case³ the rotation was even strongly to the right.

Without characterizing the sesquiterpene, Heine & Co.⁴ gave it the name of gurjunene. The product made by them had the following properties:

B. p. (?); $d_{15} = 0.920$; $\alpha_D = -136^\circ$.

See also Sesquiterpene from Minjak Lagam Balsam Oil.

15. Heveene.

Heveene¹ is obtained by the destructive distillation of caoutchouc and is but little investigated. Beilstein² includes it among the sesquiterpenes, giving its boiling point as 255–265°. It absorbs hydrochloric acid gas, forming a hydrochloride corresponding to the formula $C_{15}H_{24}HCl$, but this compound does not crystallize and decomposes readily.

16. Humulene.

Synonyms.

Diterpene (erroneously).

Terpene of poplar bud oil.

Humulene.

Based on a vapor density determination Piccard¹ in 1874 called the hydrocarbon of poplar bud oil a diterpene. In 1899 Fichter and Katz,² who identified the hydrocarbon as humulene also speak of it as the terpene of poplar bud oil. The name humulene was given to the characterized sesquiterpene by Chapman³ in 1895, after the name of the plant, *Humulus lupulus*, yielding the oil in which it was first found.

¹ Dymock, Warden and Hooper, *Pharmacographia Indica*, 1890, I, p. 193.

² List of products exhibited at Paris, 1900.

¹ This name was given to the hydrocarbon by Bouchardat (*Journ. d. Pharm.*, 1887, p. 454; *Ann.*, 27, p. 85) from *Hevea guianensis*, yielding caoutchouc.

² *Handb. d. org. Chem.*, III, p. 538.

¹ *Ber.*, 7, p. 1486.

² *Ber.*, 82, p. 3183.

³ *Journ. Chem. Soc.*, 67, p. 54.

History and General Discussion.

In 1895 Chapman⁴ isolated from oil of hops, a sesquiterpene which differed in its physical properties from any of the known sesquiterpenes, although in some respects its derivatives resembled the corresponding compounds of caryophyllene as far as then known. This sesquiterpene Chapman calls humulene. In 1899 Fichter and Katz obtained this same hydrocarbon from the oil of poplar buds.

The further characterization of caryophyllene by Schreiner & Kremers⁵ shows conclusively that humulene is quite distinct from caryophyllene. Chapman's humulene nitrosochloride melted at 164 to 165° and caryophyllene nitrosochloride at 161—163° as reported by Wallach. This led Chapman to think that the two compounds might be identical, but he could not obtain a hydrate from his sesquiterpene under the same conditions that caryophyllene readily yielded this compound. As no other compounds of caryophyllene were known at that time, further comparisons could not be made. With other known compounds now at command a comparison shows that the two sesquiterpenes cannot be identical, although the great similarity in their chemical behavior is striking. Both yield all three nitroso derivatives. Moreover, the nitrosite in each case is blue and yields an isomeric white variety. In the case of caryophyllene this white compound is obtained by the action of light, whereas the white humulene iso-nitrosite was obtained by repeated crystallizations or by heating for some time with alcohol. Even with humulene the change is possibly due more to the action of light during the process of recrystallization and boiling, than to the action of the alcohol. The great similarity in the behavior of the two compounds makes it highly probable that the blue humulene compound will react similarly on exposure to light as does the caryophyllene derivative. Whether or not a β -compound can be obtained from humulene as from caryophyllene by exposing a benzol solution of the nitrosite to light, experiment alone can decide.

A further apparent analogy between the two hydrocarbons was that both yielded only liquid addition products with hydrochloric acid, but this no longer holds, since the caryophyllene compound has been obtained in a crystalline form. However, it is also probable that a crystalline humulene dihydrochloride is obtainable in a

⁴ Journ. Chem. Soc., 67, pp. 54, 780.
⁵ Pharm. Archives, 1, p. 209 et seq.

manner similar to that by which the caryophyllene derivative was prepared.

The derivatives of the two hydrocarbons, although so similar, show by their melting points that they cannot be identical. The melting points of the nitrosochlorides, as in the case of the terpenes, cannot be used, as it is rather a decomposition point than a melting point; but the melting points of the other compounds, especially of the nitrosite and its derivatives, are characteristic. Caryophyllene nitrosite melts at 113° , whereas the corresponding humulene derivative melts at $120-121^{\circ}$; the white compound from caryophyllene nitrosite melts at $112-114^{\circ}$, humulene iso-nitrosite at $165-168^{\circ}$. The nitrolbenzylamine bases show still more conclusively the differences between these hydrocarbons. The base obtained from the nitrosochloride melts in the case of the caryophyllene compound at 167° , in the case of the humulene compound at 136° . Moreover, Chapman obtained the same piperidine base from both the nitrosate and nitrosochloride, whereas caryophyllene nitrosate and nitrosochloride yield different compounds with benzylamine.

Occurrence.

Humulene is not widely distributed. It has been found in only two oils, but these come from plants belonging to different families. It is not improbable that with further study humulene will be found in other oils as well.

Salicaceæ.

Populus nigra. Oil of Poplar Buds.

Piccard⁶ in 1873 found oil of poplar buds to boil principally between 260 and 261° and to correspond to the formula (C_5H_8). Its specific gravity was 0.9002. An analysis of a sample of oil which had stood for several weeks showed it to contain 3.48 p. c. of oxygen. In a later communication⁷ he reports the hydrocarbon as a diterpene $C_{20}H_{32}$, drawing his conclusion from a vapor density determination by Dumas' method, which would, of course, give too high a result with compounds of this nature. The fraction had a rotation of $+1.9^{\circ}$ in a 100 mm. tube.

In 1899 Fichter and Katz⁸ examined the sesquiterpene from oil of poplar buds. They obtained a fraction $132-137^{\circ}$ (13 mm.).

⁶ Ber., 6, p. 890.

⁷ Ber., 7, p. 1486.

⁸ Ber., 82, p. 3188.

263—269° (760 mm.) having the specific gravity 0.8926 and a rotation of +10° 48' in a 200 mm. tube. Although the constants of this fraction do not agree with those of humulene as found by Chapman, the preparation of characteristic derivatives showed that it contained humulene. The authors are of the opinion that a second sesquiterpene accompanies the humulene in poplar bud oil.

The humulene was identified by the preparation of a nitrosochloride, m. p. 164—170°; a blue and a white nitrosite, m. p. 127 and 172° respectively; a nitrosate, m. p. 162—163°, a nitrolpiperidine and a nitrolbenzylamine base and their hydrochlorides.

Moraceæ.

Humulus lupulus. Oil of Hops.

In 1893 Chapman⁹ described a sesquiterpene obtained by fractional distillation from oil of hops. In 1895 this was followed by two more articles in which the sesquiterpene was characterized by the preparation of several characteristic derivatives. Fraction 168—173° (60 mm.), constituting nearly two thirds of the oil used, was purified by boiling with sodium under diminished pressure and rectified by distillation. The sesquiterpene thus obtained Chapman called humulene because it differed in its properties from any of the known sesquiterpenes. The first of the articles mentioned is on oil of hops, but includes the preparation of humulene nitrosochloride by conducting nitrosyl chloride into a chloroformic solution of the sesquiterpene, as well as the preparation of the piperidine nitrolamine base from the nitrosochloride. Attempts to prepare a crystalline bromide or hydrochloride proved fruitless. The second article is on humulene derivatives in particular and includes the preparation of the nitrosate, isonitrosite, nitrolbenzylamine base and the hydrochloride of this as well as of the nitrolpiperidine base:

Preparation.

Humulene, like caryophyllene, has not been obtained in a pure state by regeneration from any of its derivatives. It is prepared by fractional distillation from oil of hops. Chapman¹¹ collected fraction 168—173° (60 mm.), corresponding to 256—261° (760 mm.). This fraction was purified by repeated distillation over sodium under diminished pressure, until the metal remained bright. Thus purified

⁹ Proc. Chem. Soc., 1893, p. 177.

¹⁰ Journ. Chem. Soc., 67, pp. 54, 780.

¹¹ Journ. Chem. Soc., 67, p. 59.

it boiled at 166—170° (60 mm.) and the analysis showed it to be free from oxygenated compounds.

Physical Properties.

Of the physical constants given, only those of Chapman can be considered as characteristic of the pure hydrocarbon. The results of Piccard and of Fichter and Katz apply to crude humulene fractions. Even the slight rotatory power noticed by Chapman is probably due to a trace of an active substance accompanying the humulene, as another sample, prepared from the same source in the same manner, had a somewhat greater rotatory power. Humulene may, therefore, be considered as being inactive when perfectly pure. The physical constants found were:

Piccard (1873): B. p. 260—261°; $d = 0.9002$; $\alpha_D = +1.9^\circ$.

Chapman (1898): B. p. 261—265° (corr.); $d_{15}^{\circ} = 0.8987$; $d_{20}^{\circ} = 0.8955$; $[\alpha]_D = +1.2^\circ$; $n_{H\alpha} = 1.4978$.

Chapman (1895): B. p. 166—170° (60 mm.), 263—266° (760 mm.); $d_{15}^{\circ} = 0.9001$, $d_{20}^{\circ} = 0.8977$; $\alpha_D = -0.5^\circ$; $n_D = 1.5021$, $n_{H\alpha} = 1.4978$.

Fichter and Katz (1899): B. p. 132—137° (13 mm.); 263—269° (760 mm.); $d_{15}^{\circ} = 0.8926$; $\alpha_D = +5^\circ 24'.^{12}$

The molecular refraction calculated from the index of refraction shows humulene to have two double bonds. This is also indicated by the bromine absorption and by the preparation of a liquid dihydrochloride.

Chemical Properties and Derivatives.

Humulene, having two double bonds, is capable of forming a tetrabromide and dihydrochloride or dihydribromide, but none of these has been obtained in a pure or crystalline condition. It also yields a nitrosochloride, a nitrosate and two nitrosites, the one blue, the other white, as well as nitrolamine bases, derived from these. Nitrosohumulene, which on reduction yields a base, has been prepared, but neither of these compounds has been obtained in a pure and crystalline condition. By means of all these derivatives, humulene is definitely characterized. The compound best suited for identification, however, is the blue nitrosite. From this the white iso-

¹² According to F. and K. this rotation is due to the presence of a second sesquiterpene.

nitrosite can be prepared and probably also the nitrol bases although Chapman and also Fichter and Katz prepared these from the nitrosochloride.

Humulene readily absorbs oxygen as was shown by Piccard,¹³ who analysed the hydrocarbon after standing a few weeks and found it to contain 3.48 p. c. of oxygen. Oxidation with cold aqueous potassium permanganate gave, according to Chapman,¹⁴ carbonic and acetic acids, together with a non-volatile acid which was not identified. When treated according to the hydration method used by Wallach for caryophyllene, no crystalline hydrate could be obtained.

Humulene dihydrochloride, $C_{15}H_{24} \cdot 2HCl$. Chapman¹⁵ prepared a liquid dihydrochloride by passing dry hydrochloric acid gas into a well cooled solution of humulene in four times its volume of ether. On evaporation of the ether a yellow oil was left, which when purified by washing with cold alcohol and drying, gave on analysis a result agreeing with the formula $C_{15}H_{25} \cdot 2HCl$. Attempts to obtain it in a crystalline condition failed, nor could it be purified by distillation under diminished pressure without the loss of large amounts of hydrochloric acid gas. The specific gravity of the impure liquid dihydrochloride was 1.063.

Humulene nitrosochloride, $C_{15}H_{24}NOCl$. Chapman¹⁶ prepared this compound by passing nitrosoyl chloride slowly into a well cooled solution of one volume of humulene in three volumes of chloroform. After a time a white crystalline substance separated, the amount of which was increased by adding cold alcohol. The precipitate was collected on a filter, washed with cold alcohol, and dried in a vacuum over sulphuric acid. It is fairly soluble in chloroform and can be obtained from this solution in a more distinct crystalline condition by the addition of alcohol.

Fichter and Katz¹⁷ prepared the nitrosochloride by treating the humulene fraction with amyl nitrite or ethyl nitrite and hydrochloric acid and recrystallized it from benzol or chloroform with the addition of methyl alcohol.

The nitrosochloride is a white finely crystalline substance and is comparatively stable. It melts at 164—165° (Chapman), 164—170°

¹³ Ber., 6, p. 890.

¹⁴ Journ. Chem. Soc., 67, p. 61.

¹⁵ Journ. Chem. Soc., 67, p. 61.

¹⁶ Journ. Chem. Soc., 67, p. 789 et seq.

¹⁷ Ber., 82, p. 3184.

(Fichter and Katz) with decomposition. With organic bases it yields nitrolamine compounds. Treatment with sodium ethylate changes it to nitrosohumulene.

Humulene nitrosate, $C_{15}H_{24}N_2O_4$. Chapman¹⁸ prepared this as follows: A mixture of 5 volumes of humulene, 5 volumes of amyl nitrite and 8 volumes of glacial acetic acid was cooled in a freezing mixture to about -15° . To this solution, a well cooled mixture of equal volumes of nitric acid and glacial acetic acid was added little by little, with constant shaking. A white crystalline substance soon formed, the mixture becoming almost solid. Alcohol was now added and after standing in the cold for about an hour, the nitrosate was collected on a force filter and washed with cold alcohol. It was purified by recrystallization from hot benzol.

The nitrosate is obtained in extremely fine, colorless needles, often forming rosettes. It is practically insoluble in alcohol and in ether, but fairly readily soluble in benzol, chloroform, and glacial acetic acid on warming. The purified nitrosate melts at 162–163° with decomposition.

Humulene nitrosite, $C_{15}H_{24}N_2O_3$. Chapman¹⁹ prepared this compound by adding to a well cooled mixture of equal volumes of humulene and light petroleum ether, a conc. aqueous solution of sodium nitrite, and lastly a volume of acetic acid equal to that of the humulene taken, little by little, with frequent shaking. From the upper hydrocarbon layer deep blue needles soon separated, which, after some hours, were collected and purified by one recrystallization from boiling alcohol.

The nitrosite crystallizes in magnificent blue needles melting at about 120° (Chapman), 127° (Fichter and Katz) with slight decomposition. It dissolves readily in hot alcohol, glacial acetic acid, ether, and chloroform, but is practically insoluble in light petroleum ether.

By repeated recrystallization from alcohol or boiling with alcohol, the blue nitrosite is gradually converted into the white iso-nitrosite, the melting point continually increasing.

Humulene iso-nitrosite, $C_{15}H_{24}N_2O_3$. The oily mother liquors obtained in the preparation of the blue nitrosite, deposited a second, and even a third crop of crystals. These, after, recrystal-

¹⁸ Journ. Chem. Soc., 67, p. 781.

¹⁹ Journ. Chem. Soc., 67, p. 782.

lization from alcohol were colorless and appear to have the same composition as the blue compound. Chapman considers this as the iso-nitrosite and the blue compound as the true nitroso derivative.

This same white compound is obtained by repeatedly crystallizing the blue nitrosite from alcohol, or simply by heating it with alcohol for several hours. During the recrystallization the crystals become paler and finally white, and the melting point gradually rises from about 120° up to 166—168°. It melts with decomposition.

That this behavior of the blue compound is probably due to the action of light, as was observed by Schreiner and Kremers for the corresponding caryophyllene compound, has already been pointed out in the general discussion.

Humulene nitrolbenzylamine, $C_{15}H_{24}(NO)NHCH_2C_6H_5$. Chapman²⁰ prepared this base by heating humulene nitrosochloride with an excess of benzylamine almost to the boiling point of the latter, and dissolving the product of the reaction in alcohol. By adding a little water the nitrolbenzylamine crystallizes out. It can be purified by recrystallization from alcohol.

This nitrol base crystallizes in bundles of very small needles radiating from a center, which melt at 136° (Chapman) 182—183° (Fichter and Katz).

Hydrochloride. By passing hydrochloric acid gas into a solution of humulene nitrolbenzylamine in dry ether, the hydrochloride of this base separates as a white, granular precipitate. It can be purified by several recrystallizations from boiling water, and melts at 187—189° with decomposition.

Humulene nitrolpiperidine, $C_{15}H_{24}(NO)NC_5H_{10}$. This compound is prepared by Chapman²¹ in precisely the same manner as that described for the benzylamine base. It is purified by recrystallization from hot alcohol.

The nitrolpiperidine base is but slightly soluble in cold, somewhat more soluble in hot alcohol. It crystallizes in the form of small, white, glistening plates. Melting point 153° (Chapman) 151 to 152° (Fichter and Katz).

Hydrochloride. The hydrochloride²² is precipitated by passing hydrochloric acid gas into an ether solution of the nitrolamine. It is purified by recrystallization from boiling water or from alcohol.

²⁰ Journ. Chem. Soc., 67, 781.

²¹ Journ. Chem. Soc., 67, p. 62.

²² Journ. Chem. Soc., 67, p. 780.

From water it crystallizes in hard nodular masses. No melting point is given.

Platinochloride ($C_{15}H_{24}NO.NC_5H_{10})_2H_2PtCl_6$. This compound is prepared²³ by mixing alcoholic solutions of platinic chloride and of the hydrochloride of nitropropiperidine. It crystallizes from alcohol in reddish needles, melting at 187–189° with decomposition.

Nitroso- or isonitroso-humulene, $C_{15}H_{24}NOH$. Fichter and Katz²⁴ obtained this compound by treating humulene nitrosochloride with sodium ethylate. It is a yellow viscous oil, distilling at 185–195° (13 mm.) and has not been obtained in a crystalline condition. By reduction a base was obtained, but it could not be prepared in a pure condition.

Chapman tried a similar reaction with humulene nitrosate but failed to get the product of the reaction in a pure form.

17. Ledene.

Ledene has not been found in nature but is obtained by dehydration from the so-called ledum camphor, found in the oil of *Ledum palustre*. Rizza¹ in 1887, recognized this so-called camphor as a sesquiterpene hydrate, and obtained from it a sesquiterpene by treatment with acetic acid anhydride. Hjelt,² in 1895, also obtained the hydrocarbon $C_{15}H_{24}$ and called it ledene.

Preparation. Ledene hydrate splits off water with great ease. Rizza prepared the sesquiterpene from ledene hydrate by heating it with acetic acid anhydride (30 g. to 5 g. of the hydrate) in a tube to 150° for 5 hours. The upper oily layer was well washed with alkali and dried with calcium chloride.

Hjelt prepared ledene by simply warming the hydrate with diluted sulphuric acid (1:1) on a water bath. The upper oily layer was distilled over with steam, separated and dried.

Properties. Ledene is a colorless liquid of a very characteristic odor and having the following properties:

Rizza (1887): B. p. 264 (752 mm.); $d_0^\circ = 0.9349$; $d_{19}^\circ = 0.9237$.

Hjelt (1895): B. p. 255°.

The chemical study of ledene is restricted to the statement that bromine is absorbed.

²³ Journ. Chem. Soc., 67, p. 781.

²⁴ Ber., 32, p. 3184.

¹ Journ. d. russ. phys.-chem. Ges., 1887, (1), p. 819; Ber., 20, Ref., p. 562.

² Ber., 28, p. 3087.

Sesquiterpene hydrate yielding ledene. Ledene hydrate. Ledene hydrate separates from the water of distillation and also from the oil of *Ledum palustre*. It was obtained by Grassmann³ as early as 1831 and was later studied by Frapp⁴ (1869), Ivanow⁵ (1876), Hjelt and Collan⁶ (1882), Rizza⁷ (1883). Rizza⁸ in 1887 and Hjelt⁹ in 1895 recognized the compound as a sesquiterpene hydrate.

Preparation. As already mentioned the hydrate separates from the oil on cooling and is also obtained from the water of distillation. It can be purified by crystallization from alcohol, benzol, ether or chloroform. It crystallizes in nice prismatic crystals from these solvents and can also be obtained in the form of long white needles by sublimation.

Properties. The physical constants of ledene hydrate are as follows:

Rizza (1883): M. p. 104—105°.

Hjelt and Collan (1882): M. p. 101°.

Hjelt (1895): M. p. 104—105°; b. p. 282—283°; $[\alpha]_D = +7.98^\circ$ in 10 p. c. alcoholic solution.

As mentioned above ledene hydrate is readily dehydrated to form ledene. Chemically ledene hydrate behaves like a tertiary alcohol. Potassium permanganate does not act upon it. No chemical derivatives have been prepared. Benzoyl chloride appears to act on the hydrate with evolution of hydrochloric acid gas and formation of an oil having the properties of ledene. Phenylcyanate acts upon it and a small amount of a substance melting at 144—145° was obtained by Hjelt, which may have been a urethane. Phosphorus chloride acts on the hydrate in ligroin solution to form a chloride which could not be obtained in a pure condition. Heated with quinoline the chloride gave rise to an oil having the boiling point of ledene, namely 255°.

³ Buchner, *Repert. für Pharm.*, 38, p. 53.

⁴ Ztsch. f. Chem., 1869, p. 350; Ber., 8, p. 542.

⁵ Russ. Ztsch. Pharm., 1876, p. 577; Jahrb. 1876.

⁶ Ber., 15, p. 2500.

⁷ Journ. d. russ. phys.-chem. Ges., 1887, (1), p. 319; Ber., 20, Ref., p. 562.

⁸ Ber., 28, p. 8087.

⁹ Prot. d. russ. phys.-chem. Ges., 1888, p. 362; Ber., 16, Ref., p. 2811

18. Patchoulene.[†]

Patchoulene does not occur in nature but is prepared by dehydrating the socalled patchouly camphor, more correctly termed patchouly alcohol by Wallach. Gal¹ in 1869 obtained from this alcohol by dehydration a hydrocarbon boiling at 248–252°, to which he assigned the formula C₁₅H₂₆. Montgolfier² in 1877 also obtained the hydrocarbon from patchouly camphor and recognized its nature as a sesquiterpene, C₁₅H₂₄. Wallach and Tuttle³ further investigated the sesquiterpene in 1894, but so far it has not been sufficiently well characterized to be designated as a chemical individual.

Preparation. Gal prepared the hydrocarbon by treating patchouly alcohol with zinc chloride. Montgolfier simply heated a solution of the alcohol in glacial acetic acid to 100° for several hours. The hydrocarbon separated in a layer, was washed and purified. Wallach and Tuttle prepared patchoulene by heating the alcohol with potassium bisulphate in a paraffin bath to 180° for one and one-half hours. The separated hydrocarbon was washed and purified in the usual way.

Properties. Patchoulene has a cedar-like odor resembling the cedrene obtained from cedarwood. It is slightly soluble in alcohol and glacial acetic acid, soluble in all proportions in ether, benzine etc., and has the following physical constants:

Gal (1869): B. p. 248–252°.

Montgolfier (1877): B. p. 252–255° (748 mm.), d₂₀° = 0.946, d_{13.5}° = 0.937; [α]_D = –42° 10'.

Wallach (1894): B. p. 254–256°; d₂₈° = 0.939; n_D = 1.50094.

The molecular refraction = 64.02; calculated for C₁₅H₂₄ = 64.45.

According to Montgolfier patchoulene does not combine with hydrochloric acid. Wallach and Tuttle report no chemical work.

Sesquiterpene hydrate yielding patchoulene. Patchouly alcohol. This alcohol, formerly called patchouly camphor,

[†] Montgolfier, C. r. 84, p. 88. Sometimes called patchoulin (Bellstein III, p. 588).

¹ Compt. rend., 68, p. 306; Ann., 150, p. 374.

² Compt. rend., 84, p. 88.

³ Ann., 279, p. 894.

⁴ Ann. 271, p. 299.

separates occasionally from patchouli oil on long standing. Gal in 1869 studied this substance and gave it the formula $C_{15}H_{28}O$. Montgolfier in 1877 recognized the compound as being isomeric with the so-called cubeb and cedar camphor and gave it the formula $C_{15}H_{26}O$. Wallach⁴ in 1892 proposed the name of patchouly alcohol.

Properties. Patchouly alcohol is soluble in alcohol and ether and crystallizes in well developed hexagonal prisms ending in six-sided pyramids. It has been found to have the following properties:

Gal (1869): M. p. 54–55°; b. p. 296°; $d_{4.5} = 1.051$; $[\alpha]_D = -95.79^\circ$ in a 19 p. c. alcoholic solution.

Montgolfier (1877): M. p. 59°; d = about 1.0; $[\alpha]_D = 118^\circ$, somewhat less in alcoholic solution.

Wallach and Tuttle (1894): M. p. 56°.

Patchouly alcohol decomposes very readily into water and hydrocarbon. The weakest dehydrating agents, such as dilute sulphuric or hydrochloric acids, or acetic acid anhydride in the cold or simply heating the compound, will readily split off water, although this is best accomplished by the method described above for the preparation of patchoulene. The behavior of patchouli alcohol shows that the hydroxyl is in a tertiary position. According to Wallach and Tuttle the compounds produced by replacing the hydroxyl by halogen are exceedingly unstable and split off halogen acid immediately.

19. Rhodiene.

Gladstone¹ obtained from oil of rhodium² (rosewood) a sesquiterpene of the following properties:

B. p. 249°; $d_{20} = 0.9042$; $\alpha_D = -11^\circ$; $n_c = 1.4911$.

It had an odor of sandalwood and roses and combines with hydrochloric acid, but no hydrochloride of definite composition could be obtained.³

20. Santalenes.

History and General Discussion.

The hydrocarbons known as α - and β -santalene have so far been found only in sandalwood oil. This oil has been investigated by a number of chemists during the last twenty years, but the literature

¹ Journ. Chem. Soc., 17, p. 1; Brühl, Ber., 21, p. 148 table.

² According to Gildemeister and Hoffmann, Die Aeth. Oele, p. 773, oil of rhodium is often a mixture of sandalwood or cedarwood oil with rose oil. There is no evidence that the oil examined by Gladstone was true oil of rhodium, distilled from *Convolvulus scoparius*.

³ Pharm. Journ., 31, pp. 687, 688.

on the subject is quite contradictory. As far as the sesquiterpenes contained in the oil are concerned, Guerbet has shown that there are two, the α - and β -santalene mentioned above. These he has definitely characterized by the preparation of several derivatives.

The nature of the oxygenated constituents is still a matter for discussion, but as some observers claim them to be sesquiterpene hydrates, yielding sesquiterpenes by dehydration, it will be well to consider them in this connection and to give a brief exposition of these conflicting views.

Chapoteaut¹ in 1882 separated oil of sandalwood into two fractions, an aldehyde boiling about 300° and having the formula C₁₅H₂₄O, and an alcohol boiling about 310°, of the formula C₁₅H₂₆O. These two compounds, when treated with phosphoric acid anhydride, yield hydrocarbons, C₁₅H₂₂ (b. p. 245°) and C₁₅H₂₄ (b. p. 260°) respectively. The first of these he considers as probably identical with cedrene, the second with the sesquiterpene of copaiba oil.

Chapman and Burgess² in 1896 isolated a fraction boiling at 301–306°, which they consider to be an aldehyde, santalal, C₁₅H₂₄O. Its properties were as follows: $d_{15}^{150} = 0.9793$, $d_{20}^{200} = 0.9761$; $[\alpha]_D = -14^{\circ} 42'$; $n_{H\alpha} = 1.5051$, $n_D = 1.5085$. By treatment with phosphorus pentoxide a hydrocarbon, C₁₅H₂₂, of the following properties, was obtained: $d_{15}^{150} = 0.9359$; b. p. 140–145° (25 mm.); $\alpha_D = +5^{\circ} 45'$. This hydrocarbon was unsaturated, combined with hydrohalogen, oxides of nitrogen and nitrosyl chloride, but no definite compounds could be obtained. The authors compared the hydrocarbon with cedrene from cedarwood oil, and conclude that it is similar to but not identical with this hydrocarbon.

The chemists of Schimmel & Co.³ prepared santalol, the alcohol of sandalwood oil, by saponification of the oil and distillation in a vacuum. The crude santalol was further purified by converting it into santalyl phthalic acid, from which it was regenerated by saponification. The product thus obtained could be separated by distillation in a vacuum into fractions which differed in rotatory power from $-7^{\circ} 20'$ to $-32^{\circ} 36'$. These chemists, therefore, concluded that santalol was a mixture of two alcohols, of which the lower boiling

¹ Bull. Soc. chim., (2) 37, p. 353.

² Proc. Chem. Soc., 1896, p. 140; Chem. News, 74, p. 95.

³ Ber. v. S. & Co., April 1899, p. 43.

one is inactive or perhaps even dextrogyrate, the higher boiling one, strongly laevogyrate. In a later report⁴ they question the formula $C_{18}H_{26}O$ for santalol, since a sample purified as stated above gave on acetylation a result corresponding to 103.5 p. c. of santalyl acetate. They conclude that santalol either has a different composition (possibly $C_{18}H_{22}O$), or else it is a mixture of nonisomeric alcohols of different composition.

The results of v. Soden and Müller⁵ published at nearly the same time, corroborate the statement of Schimmel & Co., concerning santalol being a mixture. These chemists also isolated a sesquiterpene from sandalwood oil, to which they gave the name santalene.

Guerbet⁶ in 1900 isolated from sandalwood oil two sesquiterpenes which he designated as α - and β -santalene, the latter being the same as the santalene of v. Soden and Müller. By the preparation of nitrosochlorides and nitrol piperidine bases, he was able to characterize these compounds. The oxygenated portion of the oil he found to consist of an aldehyde, santalal, and two sesquiterpene hydrates, α - and β -santalol. These santalols, when treated with phosphoric acid anhydride, yield sesquiterpenes, which Guerbet has called α - and β -iso-santalene respectively.

In the same year v. Soden⁷ published somewhat different results. He also succeeded in separating santalol into two alcohols, of which one has the formula $C_{15}H_{24}O$, and he considers it likely that the other alcohol, which has not been prepared in a pure form, will have this same composition, whereas Guerbet considered the alcohols as compounds $C_{15}H_{26}O$. If v. Soden's formula $C_{15}H_{24}O$ is correct for α - and β -santalol then the iso-santalenes obtained from them cannot be sesquiterpenes as Guerbet supposes.

The results obtained by these various investigators may be briefly summarized as follows:

Chapoteaut (1882): aldehyde, $C_{15}H_{24}O$; alcohol, $C_{15}H_{26}O$.

Chapman and Burgess (1896): Santalol (aldehyde) $C_{15}H_{24}O$.

Schimmel & Co. (1899-90): Santalol consists of two alcohols; formula possibly $C_{15}H_{22}O$, or else a mixture of nonisomeric alcohols of different composition.

v. Soden and Müller (1899): Santalene, $C_{15}H_{24}$; Santalol consists of two alcohols.

⁴ Ber. v. S. & Co., April 1900, p. 47.

⁵ Pharm. Ztg., 44, p. 258.

⁶ Compt. rend., 130, pp. 417, 1824; Bull. Soc. chim., (8) 23, pp. 218, 540.

⁷ Arch. d. Pharm., 288, p. 353.

Guerbet (1900): α - and β -santalene, $C_{15}H_{24}$; santalol (aldehyde), $C_{15}H_{24}O$; α - and β -santalol, $C_{15}H_{26}O$.

v. Soden (1900): Santalol consists of two alcohols $C_{15}H_{24}O$.

This summary clearly shows the contradictory nature of the various reports. Whether this is due to a varying composition of the oil, or to the impure compounds subjected to analysis, must be left for future work to decide. Probably none of the above investigators had an absolutely pure chemical unit under consideration, for the separation was accomplished by repeated distillation the boiling points of the alcohols being quite close together.

α - and β -Santalene.

Preparation.

The santalenes have been prepared only by fractional distillation from sandalwood oil. Guerbet⁶ prepared the sesquiterpenes as follows: Oil of sandalwood is saponified with alcoholic potash, and the product well washed with water and dried with potassium carbonate. This saponified oil is then subjected to several fractionations under diminished pressure. The oil is thus separated into groups of fractions, the first group passing between 110–180° (38 mm.) and the second between 180–200° (38 mm.). The first consists chiefly of hydrocarbons, the second of oxygenated constituents.

Separation of α - and β -santalenes. The hydrocarbon fraction from the sandalwood oil was then fractionated many times, at first in a vacuum, and later under atmospheric pressure, using a Le Bel-Henninger distilling column. Proceeding in this manner, Guerbet was able to separate the hydrocarbon fraction into two distinct sesquiterpenes, differing about ten degrees in boiling point, and yielding different derivatives. Guerbet, as stated, distinguished between them by calling the lower boiling hydrocarbon, α - and the higher boiling hydrocarbon, β -santalene.

This latter compound had already been prepared by v. Soden and Müller in 1899 by repeated fractionation of the saponified oil, and called by them, santalene.

Physical Properties.

According to Guerbet⁶ and also to v. Soden and Müller⁵ the physical properties of the santalenes are as follows:

α -Santalene.

Guerbet (1900): B. p. 252–252.5°; $d_{0^\circ} = 0.9134$; $\alpha_D = -13.98^\circ$.

 β -Santalene.

v. Soden and Müller (1899): B. p. 261–262°; $d_{15^\circ} = 0.898$; α_D = about -21° .

Guerbet (1900): B. p. 261–262°; $d_{0^\circ} = 0.9139$; $\alpha_D = -28.55^\circ$.

According to v. Soden and Müller the β -santalene is soluble in about 16 parts of 90 p. c. alcohol and readily soluble in chloroform, ether, benzene, and petroleum ether.

Chemical Properties and Derivatives.

The santalenes combine with two molecules of hydrohalogen or bromine, but no crystalline derivatives have been obtained. The hydrate and acetate are likewise liquid compounds. Guerbet succeeded in preparing nitrosochlorides of both the α - and β -santalene and from these the nitrolpiperidine base. β -santalene yielded two distinct nitrosochlorides, which were separated by fractional crystallization from alcohol. A nitrosate could not be obtained. According to Guerbet both sesquiterpenes oxidize readily in the air and give a color reaction which is quite different from that given by cadinene. Santalene when dissolved in glacial acetic acid and treated with a drop or two of sulphuric acid, gives a currant red color, which becomes deeper and finally changes to brown after standing several hours. Cadinene under the same conditions gives a fine green color, changing to blue, and on heating to red.

Santalene dihydrochloride, $C_{15}H_{24}2HCl$. H. v. Soden and Müller¹¹ mention the addition of two molecules of hydrochloric acid to santalene (β -santalene, Guerbet), but they did not obtain it in pure form. Guerbet¹² reports more fully, but also had only impure liquids under consideration, as the dihydrochlorides resisted all attempts at purification. He proceeded as follows: Dry hydrochloric acid gas was passed into a well cooled solution of santalene in ether up to saturation, and the solution allowed to stand for a time. The ether was then evaporated and the oil kept for a long time in a vacuum over caustic potash. An analysis of this impure product gave results agreeing quite well with the formula $C_{15}H_{24}2HCl$. By distillation in a vacuum the hydrochloride decomposes.

¹¹ Pharm. Ztg., 44, p. 259.

¹² Bull. Soc. chim., (3) 28, p. 541.

The rotatory power of the santalenes has suffered an inversion by the change to the dihydrochlorides:

α -Santalene dihydrochloride, $\alpha_D = +6^\circ$.

β -Santalene dihydrochloride, $\alpha_D = +8^\circ$.

Santalene nitrosochlorides, $C_{15}H_{24}NOCl$. H. v. Soden and Müller¹³ did not succeed in the preparation of this derivative. Guerbet¹⁴ states that the general method of Wallach gave but an insignificant yield. He obtained a yield of about 50 p. c. by dissolving the santalene in petroleum ether and adding to this a solution of nitrosyl chloride in the same solvent, keeping the mixture at a low temperature.

α -Santalene nitrosochloride. α -Santalene yields only one nitrosochloride. It is crystalline, insoluble in alcohol, and only slightly soluble in ordinary ether, but very soluble in petroleum ether and in benzol. From a solution in the latter solvent it is deposited in small, short prismatic crystals, melting at 122° with decomposition. It yields a nitrolpiperidine base.

β -Santalene nitrosochlorides. β -Santalene yields two isomeric nitrosochlorides. Both are soluble in alcohol, which fact distinguishes them from α -santalene nitrosochloride. They are also more stable when heated and can be melted without decomposition.

The two isomeric β -santalene nitrosochlorides are separated by fractional crystallization from 95 p. c. alcohol. The nitrosochloride least soluble in the alcohol, crystallizes in large striated tablets and melts at 152° ; the other, present in much larger quantity, crystallizes in prismatic needles, melting at 106° . Both yield nitrolpiperidine bases.

Santalene nitrolpiperidines, $C_{15}H_{24}(NO)NC_5H_{10}$. Guerbet obtained three distinct nitrolpiperidine bases by treating the three nitrosochlorides with piperidine.

α -Base. This was obtained from the α -santalene nitrosochloride by treating with piperidine in benzene solution. It is very soluble in alcohol, from which it crystallizes in fine needles melting at $108-109^\circ$.

β -Bases. There are two β -bases obtained from the two β -nitrosochlorides described above. Both are soluble in alcohol and melt at 101° and $104-105^\circ$ respectively.

¹³ Pharm. Ztg., 44, p. 259.

¹⁴ Bull. Soc. chim., (3) 28, p. 541.

Santalene acetates, $C_{15}H_{24}C_2H_4O_2$. According to Guerbet, when α - and β -santalenes are heated to 180–190° in sealed tubes with glacial acetic acid, the sesquiterpenes slowly combine with it to form acetates. Guerbet obtained, however, a yield of only 2.5 p. c. The acetates are colorless liquids of agreeable odor.

α -Acetate boils at 164–165° (14 mm.).

β -Acetate boils at 167–168° (14 mm.).

Santalene hydrate, $C_{15}H_{25}OH$. Guerbet could not prepare a hydrate of α - and β -santalene as had been done by v. Soden and Müller¹⁵ with santalene (β -santalene, Guerbet). These chemists prepared a hydrate by a method similar to that described for caryophellene hydrate (see this). From the product of the reaction these chemists isolated a small amount of an alcohol, $C_{15}H_{25}OH$. It had an odor resembling cedarwood oil and the following constants:

B. p. 160–165° (7 mm.); $d_{15}=0.978$; optically inactive.

α - and β -Iso-Santalene:

Guerbet¹⁶ obtained α - and β -iso-santalene by the dehydration of α - and β -santalol respectively. The compound corresponding to the α -santalol of Guerbet (and possibly also β -santalol) is, however, considered as an alcohol of the formula $C_{15}H_{24}O$, by v. Soden.¹⁷ Should this be true, the hydrocarbons obtained by dehydration from these alcohols, would have the formula $C_{15}H_{22}$, and would, therefore, not fall into the class of the sesquiterpenes.

According to Guerbet, phosphoric acid anhydride acts very violently on the santalols, but by cooling with ice water before adding the dehydrating agent, the reaction can be moderated. At best the yield of hydrocarbon is small, amounting to about 42 p. c. of the crude hydrocarbon. This crude hydrocarbon is purified by rectification under reduced pressure.

The iso-santalenes are colorless liquids of a terebinthinate odor and have the following properties:

α -Iso-santalene; b. p. 255–256°; $a_D=+0.2^\circ$.

β -Iso-santalene; b. p. 259–260°; $a_D=+6.1^\circ$.

Alcohols yielding the iso-santalenes. Santalol (Gonorol).¹⁸ Schimmel & Co.¹⁹ prepare santalol by heating East Indian

¹⁵ Pharm. Ztg., 44, p. 259.

¹⁶ Bull. Soc. chim., (3) 28, p. 543.

¹⁷ Arch. d. Pharm., 238, p. 358.

¹⁸ Trade name given by Heine & Co.

¹⁹ Ber v. S. & Co., April 1899, p. 43.

sandalwood oil with an equal weight of phthalic acid anhydride and benzene for one hour to 80° on a water bath. The acid esters formed are combined with alkali and dissolved in much water. This aqueous solution is then shaken three times with ether to remove the non-alcoholic constituents. The acid esters are then again liberated by treating with dilute sulphuric acid and after separating they are saponified with alcoholic potash and washed with water.

Guerbet²⁰ saponified the oil and separated it into two fractions by several distillations under diminished pressure, as already described under santalene. The higher boiling fraction was then treated in a manner similar to that employed by Schimmel & Co.

H. v. Soden²¹ also saponified the oil and then separated the santalol from the sesquiterpenes by repeated distillation under diminished pressure.

Separation into α - and β -santalol. Schimmel & Co., and also v. Soden and Müller, showed that santalol was a mixture of alcohols. Guerbet²² succeeded in separating santalol into two alcohols, $C_{15}H_{26}O$, which he considered as isomeric, by repeated fractionation under diminished pressure. These alcohols Guerbet distinguished as α - and β -santalol, H. v. Soden²³ separated the oil into a number of fractions by repeated distillation. In this way he was able to effect a partial separation of α - and β -santalol. The β -santalol was not prepared in a purer condition, but the crude α -santalol was purified by converting it into an acid ester of phthalic acid, much in the same manner as already described for santalol, and then fractionating under diminished pressure.

The physical properties of these alcohols are as follows: The results of Guerbet and v. Soden only are given as these chemists had undoubtedly purer products under consideration than earlier workers, and also because the alcohols having these specific properties were used in the preparation of the iso-santolenes described above.

α -Santalol.

Guerbet: formula $C_{15}H_{26}O$; b. p. 162–163° (13 mm.), 300–301° (760 mm.); $d_0^{\circ}=0.9854$; $\alpha_D^{\circ}=-1.20^{\circ}$.

v. Soden: formula $C_{15}H_{24}O$; b. p. 155° (8 mm.), 301–302° (752 mm.); $d_{15}^{\circ}=0.977$; $\alpha_D^{\circ}=+1^{\circ}40'$ to $2^{\circ}4'$.

²⁰ Bull. Soc. chim., (8) 28, p. 218.

²¹ Arch. d. Pharm., 238, p. 357.

²² Bull. Soc. chim., (8) 28, p. 23, pp. 219, 543.

²³ I. c.

β -Santalol.

Gourbet: formula $C_{15}H_{26}O$; b. p. 170–171 (14 mm.), 309–310 (760 mm.); $d_0^{\circ} = 0.9868$; $a_D = -56^{\circ}$.

21. Sesquiterpene of Ageratum Oil.

The oil distilled by van Romburgh* from the fresh herb of *Ageratum conyzoides* has the sp. gr. 1.015 at 27.5°; $a_D = -2.75^{\circ}$ and boils at about 260°. The oil probably contains compounds belonging to the group of sesquiterpenes.

22. Sesquiterpene from Amyrol.

H. v. Soden and Rojahn¹ obtained a sesquiterpene from amyrol by the action of acid agents, but no statements as to its properties are made.

Amyrol. This sesquiterpene alcohol is obtained from West Indian sandalwood oil, which is not a true sandalwood oil, but a product of *Amyris balsamifera*, nat. ord. *Rutaceæ*. Its similarity to East Indian sandalwood oil gave rise to the supposition that it also contained sesquiterpene alcohols. This suspicion was verified by Duliére² in 1897 who acetylated the oil and then saponified the acetic esters formed. On the basis of his results he calculates 42 p. c. of alcohol as santalol.

In 1900 v. Soden³ isolated from the oil by fractional distillation under diminished pressure, an alcohol $C_{15}H_{25}OH$, which was different from santalol, and for which he proposed the name of amyrol. It had a specific gravity of 0.980–0.982 at 15° and a rotation of about +27°; it boiled at 299–301 (748 mm.), 151–152° (11 mm.). Attempts to prepare the phthalic acid ester failed, water being split off and a sesquiterpene generated. The acetylation is not quantitative for the same reasons.

In a second communication by v. Soden and Rojahn⁴ amyrol is reported as consisting of two sesquiterpene alcohols. The two alcohols were separated by repeated fractional distillation. The higher boiling alcohol has the composition $C_{15}H_{25}OH$. It is very viscous and has a peculiar aromatic odor and the following properties:

$$d_{15}^{\circ} = 0.987; a_D = +36^{\circ}; \text{b. p. } 299^{\circ}.$$

* Ber. v. S. & Co., April 1898, p. 57.

¹ Pharm. Ztg., 145, pp. 229, 878.

² Bull. d. l'Academie roy. d. Med. d. Belgique, (4), 9, p. 769.

³ Pharm. Ztg., 45, p. 229.

⁴ Pharm. Ztg., 45, p. 878.

With dehydrating agents, such as mineral acids, etc., it yields a sesquiterpene. The lower boiling alcohol appears to have the composition $C_{15}H_{28}OH$ and to be optically inactive. Distilled with acid agents, a hydrocarbon results, which they suspect to be l-cadinene.

23. Sesquiterpene of Angelica Root Oil.

Beilstein and Wiegand¹ in 1882 obtained from the oxygen containing portions of angelica root oil, boiling above 200°, by treatment with metallic sodium, a fraction which boiled for the greater part at about 250° and corresponded to the formula (C_5H_8).

In 1896 Ciamician and Silber² subjected the higher boiling fractions of angelica root oil to an examination. One of the fractions on standing deposited crystals melting at 74—77°. The fraction was distilled in a vacuum and then saponified with alcoholic potassa. The unsaponified portion boiled between 240 and 270° and had the characteristic odor of the sesquiterpenes. It was not further investigated.

24. Sesquiterpene of Basilicum Oil.

According to van Romburgh³ the variety *Selasih besar* of *Ocimum basilicum*, yields an oil which contains, besides methyl-chavicol, eugenol and an olefinic terpene, called ocimene, a higher boiling compound which probably is a sesquiterpene. Further work on this body is promised.

25. Sesquiterpene of Calamus Oil, Japanese.

According to Schimmel & Co.⁴ the oil of Japanese calamus from *Acorus spuriosus* boils between 210—290°. The higher boiling portions are described as having a "peculiar sesquiterpene odor." Possibly this hydrocarbon is identical with calamene from ordinary calamus oil.

26. Sesquiterpene of Carline Thistle Oil.

Carline thistle yields about 2 p. c. of a volatile oil which boils for the greater part between 265—300°. Its sp. gr. is 1.03 at 18°. By distillation in a vacuum and treatment with metallic sodium, Semmler⁵ in 1889 isolated a hydrocarbon belonging to the series

¹ Ber., 15, p. 1741.

² Ber., 29, p. 1811.

³ Koninklijke Akademie von Westenschappen te Amsterdam, 1900, p. 446; Ber. v. S. & Co., Apr. 1901, p. 11.

⁴ Ber., 8, & Co., April 1889, p. 7.

⁵ Chem. Ztg., p. 1158; Pharm. Ztg., 1888, p. 648; Jahresb. f. Pharm., 1889, p. 857.

(C₅H₈), boiling at 250—253° under ordinary pressure and having a vapor density of 6.78 and 6.82. Its specific gravity is very low for a sesquiterpene, being only 0.8733 at 22.8°. The hydrocarbon which is present to the extent of 12 p. c. in the crude oil, readily absorbs the halogens and hydrohalogens; conc. nitric acid acts very violently upon it. No crystalline derivatives of any kind were obtained.

These data are insufficient to establish its relationship with zingiberene but, if not identical with the latter, it doubtless belongs to the same group of sesquiterpenes.

27. Sesquiterpene from Caryophyllene Dihydrochloride.

Schreiner and Kremers¹ attempted to regenerate caryophyllene from its dihydrochloride in a manner similar to that employed for the regeneration of cadinene from its dihydrochloride. Instead of caryophyllene they obtained an oil of different properties. When some of the oil, dissolved in petroleum ether, was treated with a saturated solution of sodium nitrite and glacial acetic acid, the petroleum ether layer turned a beautiful blue, as it does in the case of the nitrosite of caryophyllene, but no crystals could be obtained. Attempts to prepare other caryophyllene derivatives likewise failed. Its physical properties are also different from those of caryophyllene, especially its optical rotation. Nor does it appear to be identical with clovane, generated by Wallach from caryopoyllene hydrate. Wallach states that clovane is not capable of uniting with nitrosyl chloride, and it is, therefore, also incapable of uniting with the oxides of nitrogen. A comparison of the sesquiterpene generated from caryophyllene dihydrochloride with clovane and caryophyllene is given in the following table:

	Caryophyllene.	Sesquiterpene generated from caryophyllene dihydrochloride.	Clovane.
Sp. gr.....	0.9039 (20°)	0.9191 (20°)	0.930 (18°)
Index of refraction	1.40976	1.49801	1.50066
Rotation	-8.96°	-35.39°	

Whether this sesquiterpene is an individual compound or a mixture of caryophyllene with another sesquiterpene cannot be stated.

¹ Pharm. Archives.

The indications are, however, that an inversion with the possible production of an isomer has taken place.

28. Sesquiterpenes of Cascarilla Oil.

In 1899 Thoms¹ reports on an oil of cascarrilla investigated by Fendler, who found 10.5 p. c. of a sesquiterpene boiling at 255–257° and 33 p. c. of a sesquiterpene boiling at 260–265°, as well as 11 p. c. of an alcohol $C_{15}H_{28}GH$ boiling at 280–290°.

Fendler² himself makes a more detailed report. The lighter sesquiterpene is a light yellow oil of the following properties:

$d_{20}^{\circ} = 0.911$; $[\alpha]_D = +23.49^{\circ}$; b. p. 178–181° (100 mm.), 255–257° (760 mm.).

Analysis shows the compound to contain some oxygen, but attempts to remove this failed. Attempts to prepare a hydrochloride, a bromide, and a nitrosoite likewise failed.

The heavier sesquiterpene is a light yellow oil and is the principal constituent of the oil. It has the following properties:

B. p. 185–190° (100 mm.), 260–265 (760 mm.); $d_{20} = 0.924$; $[\alpha]_D = +7.36^{\circ}$.

Analysis revealed the presence of oxygenated constituents also in this fraction. A molecular weight determination by the freezing point method, gave 195; calc. for. $C_{15}H_{24} = 204$.

Concerning the sesquiterpenes Fendler remarks: "Diese völlig zu reinigen und zu charakterisieren resp. zu identifizieren, ist nach dem heutigen Stande der Kenntniss der Terpene noch unmöglich. Nach ihren Eigenschaften, welche von denen der bekannteren Sesquiterpene abweichen, ist anzunehmen, dass sie sich später vielleicht als neue, dem Cascarrillöl eigentümliche Körper erweisen werden; möglicherweise sind sie auch mit einem oder dem anderen der zahllosen, teils benannten, teils unbenannten, aber noch wenig charakterisierten Sesquiterpene identisch."

29. Sesquiterpene of Celery Seed Oil.

In 1897 Ciamician and Silber³ examined the distillation residue and the last runnings obtained in the preparation of celery seed oil. The ethereal solution of the oil was treated first with cold and then with hot alkali, which separated phenols and acids. The insoluble

¹ Apoth. Ztg., 14, p. 562.

² Arch. d. Pharm., 238, 688.

³ Ber., 10, p. 496.

oil was found to amount to about 25 p. c. in the case of the distillation residue and 80 p. c. in the case of the last runnings. It boils for the greater part between 262 and 269°. A test for phenol esters gave a negative result and an analysis gave results that agreed with the formula $C_{15}H_{24}$. No solid hydrochloride could be obtained by treating with gaseous hydrochloric acid in ether solution. The sesquiterpene was not further investigated.

29. Sesquiterpenes of Citronella Oil.

A very exhaustive investigation of citronella oil was made by the chemists of Schimmel & Co.¹ in 1899 by fractionating 100 kilos of oil by steam distillation. The 17th fraction (5 kilos of oil) consisted mainly of methyl eugenol and sesquiterpene, and a small amount of geraniol. The latter was removed by fractional distillation up to 146° under 18 mm. pressure. The residue was then shaken out with 60 p. c. alcohol. Methyl eugenol is soluble in 10 parts of 60 p. c. alcohol, whereas the sesquiterpene is but sparingly soluble in this mixture. This treatment was repeated eight times with 70 p. c. alcohol and the residue subjected to distillation under diminished pressure. In this way a fraction of nearly constant boiling point was obtained, which had the following properties:

B. p. 157° (15 mm.); $d_{15}^{\circ}=0.8643$; $\alpha_D=+1^{\circ}28'$; $n_D=1.5184$.

Under ordinary pressure the compound boils between 270—280° with much decomposition. An elementary analysis showed that some oxygen was still present, but its properties clearly showed the compound to be a sesquiterpene.

This sesquiterpene has the lowest specific gravity known of any member of this class of hydrocarbons. A calculation, based on the index of refraction, as to the number of double bonds present, indicates four double bonds. The compound appears, therefore, to be an olefinic sesquiterpene. The hydrocarbon corresponds in its properties to this supposition. It resinifies on standing for only a day, halogens and hydrohalogens produce immediate decomposition even in a freezing mixture: dilute permanganate solution yields only carbonic acid, oxalic acid and a glycol-like body, soluble in water. The hydration with acetic and sulphuric acids (0.1 p. c. of the latter) was very incomplete, the product of the reaction showing a saponification number of only 43.6.

¹ Ber. v. S. & Co., Oct. 1899, p. 12.

Although no characteristic derivatives of this sesquiterpene could be prepared, it is nevertheless quite certain that it is different from any of the known members of this group in its physical properties.

The 18th fraction (also 5 kilos) obtained in the fractionation of the oil by steam distillation was treated in the same way with 70 p. c. alcohol and the washed product distilled under diminished pressure. A second sesquiterpene leaving the following properties was thus obtained:

B. p. 272–275° (700 mm.), 170–172° (16 mm.); $d_{15}^{\circ} = 0.712$; $\alpha_D = +5^{\circ}50'$.

On account of the slight difference in boiling point (about 8°) it was not possible to completely free the heavier sesquiterpene from the lighter compound, and the above specific gravity is, therefore, a little low. No chemical work on this heavier sesquiterpene is reported, and its identity with any of the known sesquiterpenes cannot be established by means of the data at hand.

30. Sesquiterpene of Copiba Balsam Oil, African.

Umney¹ has examined the oil distilled from the so-called African copaiba balsam. The sp. gr. of the oil is 0.918 and it boils between 260–273°. Its rotation in a 200 mm. tube is +20°42'. No crystalline hydrochloride could be obtained by passing dry hydrochloric acid gas into the oil, as has been stated to be the case by Soubeiran and Capitaine² with Maracaibo oil. Under similar treatment Umney has, however, also failed to get crystals of a hydrochloride from the Maracaibo variety, which result agrees in this respect with the experiments of Brix.³

The fraction boiling at 264° was subjected to the hydration method used by Wallach for identifying the sesquiterpene of ordinary copaiba balsam oil with caryophyllene.⁴ Umney was unable to get a crystalline hydrate from the African variety, although fraction 260° of a South American copaiba oil yielded a small amount of a crystalline hydrate, identical with caryophyllene hydrate.

The failure to get a crystalline hydrate, also the rotatory power of the oil, seem to indicate the absence rather than the presence of caryophyllene. The fact that this sesquiterpene has been identified in the American varieties, makes it highly desirable that this oil be subjected to the more modern tests. It is not improbable that we have here a dextrogyrate caryophyllene.

¹ Pharm. Journ., (8), 22, p. 450; 24, p. 215.

² Journ. Pharm., 26, p. 70.

³ Monatsbette, 2, p. 507.

⁴ See caryophyllene hydrate.

31. Sesquiterpene of Cubeb Oil.

According to Oglialoro¹ and also Schmidt,² oil of cubebs contains, besides cadinene, a sesquiterpene of lower boiling point (262—263°) and lower rotatory power, which does not combine with hydrochloric acid. For discussion see cadinene in cubeb oil.

32. Sesquiterpene of Cypress Oil.

According to Schimmel & Co.³ the oil from the leaves and twigs contains pinene, and "probably sylvestrene and a sesquiterpene." No data whatever are given.

Cypress camphor. From the last running of the oil distilled from the leaves and young branches of *Cupressus sempervirens* a crystalline substance occasionally separates.⁴ This "cypress camphor" is probably a sesquiterpene hydrate, as it resembles cedar camphor or cedrol, from which it differs, however, by being optically inactive. It may possibly be the optically inactive modification of cedrol. From alcohol the compound crystallizes in fine needles, from petroleum ether in compact crystalline masses.

33. Sesquiterpene of Erechthites Oil.

Beilstein and Wiegand⁵ found fraction 240—310° of erechthites oil, after distillation from sodium, to correspond to the composition C₅H₈. The high boiling point would seem to indicate a sesquiterpene.

Power⁶ found the oil to give Wallach's color reaction for cadinene.

34. Sesquiterpene of Garlic Oil.

Beckett and Wright⁷ found in garlic oil a sesquiterpene, C₁₅H₂₄, boiling at 253.9° but Semmler⁸ did not find this compound in the crude oil examined by him.

¹ Ber., 8, p. 1357.

² Arch. d. Pharm., 191, p. 22.

³ Ber. v. S. & Co., Oct. 1894, p. 71.

⁴ G.-H.-K., The volatile oils, p. 269.

⁵ Ber., 15, p. 2852.

⁶ Pharm. Rundschau, 5, p. 202.

⁷ Jahresh. f. Chem., 1876, p. 398.

⁸ Arch. d. Pharm., 280, p. 441.

35. Sesquiterpene of Hemlock Needle Oil.

Bertram and Walbaum¹ report the presence of a sesquiterpene in oil of hemlock, but do not identify it.

Schimmel & Co.² in 1893 mention cadinene as a constituent of this oil, without, however, giving any proof or reference. The same is done by Heusler.³ Gildemeister & Hoffmann⁴ still mention the sesquiterpene as undetermined.

36. Sesquiterpene of Hemp Oil.

Personne⁵ in 1857 isolated two hydrocarbons from the oil of hemp. These had the formulas C₁₂H₁₄ (?) and C₁₈H₂₀. The latter hydrocarbon he called *cannabene*. The work of Valenta and also of Vignola show cannabene to have been an impure sesquiterpene.

Valenta⁶ in 1880 investigated an oil distilled from Italian hemp. The oil consisted principally of a sesquiterpene which had the following properties:

B. p. 256—258°; d₀[°] = 0.9289; [α]_D = -10.81°.

With hydrochloric acid it formed a solid derivative.⁷ The oil from the male inflorescence of *Cannabis gigantea* is said to contain the same sesquiterpene.

The oil of hemp distilled by Vignolo⁸ in 1895 boiled between 248 and 268°. By repeated treatment with sodium, he obtained an oil boiling at 256°. Its sp. gr. was 0.897 at 15.3° and showed a slight rotation to the left in a chloroform solution. The compound was identified as C₁₅H₂₄ by analysis and vapor density. With bromine it yields a solid compound, but evidently undergoes decomposition as hydrobromic acid is given off. With hydrochloric acid it yielded no solid hydrochloride.

Wood, Spivey and Easterfield⁹ in 1896 examined the resin of Indian hemp. From the oil they separated a sesquiterpene, which after treatment with sodium had the following properties:

B. p. 258—259°; d₁₈[°] = 0.898; [α]_D = -8.6°.

¹ Arch. d. Pharm., 231, p. 295.

² Ber. v. S. & Co., Oct. 1893, Suppl. p. 21.

³ Die Terpene, p. 168.

⁴ G.-H.-K., The volatile oils, p. 264.

⁵ Journ. de Pharm., 31, p. 48.

⁶ Gazz. chim., 10, p. 479; 11, p. 191; Ber. 13, p. 2431; 14, p. 1717.

⁷ G.-H.-K., The volatile oils, p. 338.

⁸ Gazz. chim., 25, I, p. 110; Ber., 27, Ref. p. 406; Ber. v. S. & Co., Oct. 1895, p. 57.

⁹ Journ. Chem. Soc., 69, p. 589.

This sesquiterpene absorbed hydrochloric acid and bromine but no crystalline derivatives were obtained.

The properties of the sesquiterpene of hemp oil agree best with those of impure caryophyllene.

37. Sesquiterpene of *Kampferia Galanga* Oil.

Van Romburgh obtained from the oil of *Kampferia galanga* a bluish green fraction boiling at 150° in a vacuum which probably consists of a sesquiterpene.¹

38. Sesquiterpene of Kesso Root Oil.

Bertram and Gildemeister² obtained from oil of kesso root a fraction which boiled between 260 and 280°. It is described as a colorless liquid having a decided sesquiterpene odor. Attempts to prepare a hydrochloride failed. The highest boiling portions consisted of a blue oil.

39. Sesquiterpene of Laurel Berry Oil.

Blas³ isolated from the oil of laurel berries by treatment with solution of caustic potassa a hydrocarbon which, after distillation from sodium in an atmosphere of hydrogen, had the following properties:

B. p. 250°; $d_{15}^{\circ} = 0.925$; $\alpha_D = -7.23^{\circ}$.

Analysis agreed with the formula C₁₅H₂₄. Blas points out that the rotatory power agrees best with that of the hydrocarbon from oil of rhodium, which Gladstone determined as -11°.

The physical constants of this hydrocarbon appear to agree best with those of caryophyllene as shown by the following tabulation of constants:

	B. p.	Sp.gr.	<i>t. d.</i>
Caryophyllene	136—137° (Schreiner & Kremers)	0.9030 (20 mm.)	-8.09°
Sesquiterpene	250°	0.925	-7.23°
Caryophyllene	258—260° (Wallach)	0.9085	active

The question might readily be decided by means of the nitrosite reaction for this hydrocarbon, if some of the oil could be obtained.

¹ Ber. v. S. & Co., Oct. 1900, p. 88.

² Arch. d. Pharm., 228, p. 486.

³ Ann., 184, p. 1.

40. Sesquiterpene of Lavender Oil.

Seminler & Tiemann¹ obtained a small amount of a sesquiterpene boiling at 130° under 15 mm. pressure from English lavender oil. No other properties are given.

41. Sesquiterpene of Lemon Oil.

According to Oliveri² the high boiling fractions of lemon oil contain a sesquiterpene, having the following properties:

B. p. 240—242°; $d_0^{\circ} = 0.9847$.

The tetrabromide and dihydrochloride of this body are liquids.

42. Sesquiterpene of Linaloe Oil.

Barbier and Bouveault³ obtained from the saponified Mexican linaloe oil, after repeated distillation under a pressure of 10 mm. a fraction boiling between 130 and 140°. By treatment with sodium and rectification in a vacuum they isolated a hydrocarbon boiling at 135—136° (10 mm.) and corresponding to the formula C₁₅H₂₄ as was shown by analysis and molecular weight determination. The sesquiterpene absorbs four atoms of bromine and contains, therefore, two double bonds.

The quantity of hydrocarbon found in the oil is about 3 p. c. although the authors state that the amount is variable as another sample from an equally authentic source, contained very little of this hydrocarbon. The almost total absence of physical constants and chemical work is to be regretted.

43. Sesquiterpene of Long Pepper Oil.

The oil of long pepper was distilled by Schimmel & Co.⁴ in 1890. It is described as having a mild taste and an odor reminding of ginger. It boils between 250—300° and has a specific gravity of 0.861 at 15°.

The high boiling point and low specific gravity would seem to indicate a hydrocarbon of the sesquiterpene series. The data given are insufficient for making a comparison with the properties of zingiberene, but it doubtless belongs to the same class of the sesquiterpenes as the latter.

¹ Ber., 25, p. 1187.

² Gazz. chim., 21, p. 318; Ber., 24, Ref. p. 624.

³ Compt. rend., 121, p. 168.

⁴ Ber. v. S. & Co., 1890, p. 48.

44. Sesquiterpene of Minjak-Lagam Balsam Oil.

Minjak-Lagam balsam is closely allied to gurjun balsam and it is not improbable that the sesquiterpene from this oil is identical with the sesquiterpene from gurjun balsam oil (see Gurjunene).

Haussner¹ in 1883 examined the volatile oil distilled from the balsam with water vapor. The oil was separated, dried and distilled in an atmosphere of carbon dioxide. It had the following properties:

B. p. 249—251°; $d_{15}^{\circ} = 0.923$; $\alpha_D = -9.9^{\circ}$.

The oil corresponded to the composition $C_{15}H_{24}$, although Haussner gives the formula $C_{20}H_{32}$, based on a vapor density determination by Hoffmann's method, which, no doubt, gives too high a result at the temperature of boiling diphenylene, viz. 290°. Exposed to air it readily resinifies.

Trihydrochloride. Haussner succeeded in preparing a trihydrochloride of this sesquiterpene by passing dry hydrochloric acid gas directly into the oil contained in U-tubes kept cold by a freezing mixture. The oil became dark violet and very viscous. After standing for some time in the freezing mixture, the heavy oil was found to be interspersed with crystals. These were separated by pressing on filter paper. The oil absorbed by the paper was taken up with alcohol, and after evaporating the solvent it was again treated with hydrochloric acid gas. A second crop of crystals was thus obtained. The crystals were purified by several crystallizations from alcohol. The analysis agreed with the formula $C_{15}H_{24} \cdot 3HCl$ or $C_{20}H_{32} \cdot 4HCl$ as Haussner considers it.

The trihydrochloride is soluble in alcohol, ether, benzol, and carbon disulphide. From cold alcohol it separates in long (3 cm.) white needles, melting at 114°. From hot alcohol it separates in felt-like crystals.

The formation of this trihydrochloride is rather surprising, as it would indicate the presence of three double bonds in the sesquiterpene. For this, its specific gravity is, however, rather high. It is to be regretted that the index of refraction was not determined so that the number of double bonds might have been calculated from this physical constant.

Beyond the preparation of the trihydrochloride Haussner obtained no positive results, although he tried the action of the halogens on the oil.

¹ Arch. d. Pharm., 221, p. 245.

45. Sesquiterpene of Peppermint Oil, English.

Flückiger and Power¹ separated from dementholized Mitcham oil of peppermint, a fraction which after repeated rectification over metallic sodium had the following properties:

B. p. 255–260°; $d_{21}^{\circ} = 0.912$; $\alpha_D = +9^{\circ} 2'$.

Analysis agreed fairly well with the formula $C_{15}H_{24}$. Although the oil was dextrogyrate it is possible that it was identical with the cadinene found in the American oil by Schimmel & Co.²

46. Sesquiterpene of Peppermint Oil, Japanese.

Beckett and Wright³ examined Japanese oil of peppermint and, after separating the menthol, they obtained a fraction boiling at 245–253°. This they supposed to be a compound $C_{30}H_{50}O$ formed by splitting off two molecules of water from three molecules of the compound $C_{10}H_{18}O$ (menthone?)



It is more probable that the fraction consisted of a sesquiterpene (found in both English and American oils) mixed with an oxygenated constituent.

47. Sesquiterpene of Pimenta Oil.

In 1864, Oeser⁴ investigated pimenta oil. He dissolved the oil in caustic potash and then treated it with water. On heating slightly, an indifferent oily layer separated. This oil, after having been dried and rectified, had the following properties:

B. p. 235°; $d_8^{\circ} = 0.98$; $[\alpha]_D = -0.49^{\circ}$.

Analysis showed it to have the formula $(C_5H_8)_x$ and on account of its high boiling point Oeser gave it the formula $C_{15}H_{24}$. Oeser further thinks that it is identical with the hydrocarbon found by Williams⁵ and earlier by Brüning⁶ and by Ettling⁷ in oil of cloves. This, however, appears not to be the case, as the specific gravity of the hydrocarbon from cloves, now known as caryophyllene, is much less than that of the hydrocarbon from pimenta oil. A more thorough investigation of this hydrocarbon would doubtless prove interesting.

¹ Pharm. Journ., (2), 11, p. 22; Arch. d. Pharm., 218, p. 222.

² Ber. v. S. & Co., Apr. 1894, p. 42.

³ Journ. Chem. Soc., 1876, I, p. 8.

⁴ Ann., 181, p. 277.

⁵ Ann., 107, p. 242.

⁶ Ann., 104, p. 202.

⁷ Ann., 9, p. 68.

48. Sesquiterpene of Poplar Bud Oil.

Fichter and Katz¹ in 1899 found the sesquiterpene fraction of poplar bud oil to consist chiefly of humulene, but as the yield of humulene derivatives was smaller than obtained from the sesquiterpene of hop oil, and also because their fraction was optically active, whereas the humulene of Chapman² is inactive, they conclude that another sesquiterpene accompanies the humulene in oil of poplar buds. See under humulene.

49. Sesquiterpene of Sage Oil, English.

Sugiura and Muir³ in 1878 report on the examination of a small sample of "absolutely pure sage oil" (English). It consisted for the most part of a sesquiterpene having the following properties:

B. p. 264—270°; $d_{10}^{\circ}=0.9198$, $d_{24}^{\circ}=0.9072$; $\alpha_D=+3^{\circ} 14'$.

It had a dark emerald green color and did not form a stable hydrochloride.

In 1880 Muir⁴ confirms his previous work and states that large quantities of cedrene are present in English sage oil distilled from the leaves. This time he gives the boiling point as 260°.

Although Muir calls the sesquiterpene cedrene, it is quite different in its properties from the cedrene obtained from cedarwood oil. There can be but little doubt that Muir used the name cedrene in the sense suggested by Beckett and Wright⁵ in 1876, who applied the designation "cedrenes" to all hydrocarbons of the formula $C_{15}H_{24}$.

50. Sesquiterpene from Santonin and Santonin Derivatives.

Cannizzaro and Amato⁶ in 1874 found that when santonic acid, $C_{15}H_{20}O_4$ is treated with hydriodic acid, there results a hydrocarbon, $C_{15}H_{26}$ and an iodide $C_{15}H_{25}I$. This iodide boils at 143—145° under 5 mm. pressure. Distilled at ordinary pressure, it decomposes largely into hydriodic acid and a sesquiterpene, $C_{15}H_{24}$.

According to Andreucci⁷ a liquid hydrocarbon of the formula $C_{15}H_{24}$ (or $C_{14}H_{22}$) boiling at 247° results besides santonic acid, when santonin, $C_{15}H_{18}O_8$, is reduced by heating with stannous chloride and tin in hydrochloric acid solution.

¹ Ber., 82, p. 8183.

² Journ. Chem. Soc., 67, pp. 54, 780.

³ Journ. Chem. Soc., 88, p. 297; Pharm. Journ., 87, p. 994.

⁴ Journ. Chem. Soc., 87, p. 678.

⁵ Journ. Chem. Soc., (8), 1, p. 6.

⁶ Ber., 7, p. 1104.

⁷ Ber., 26, Ref. p. 599.

51. Sesquiterpene of Spike Oil.

Bouchardat¹ states that the fractions of spike oil boiling higher than 160° approach more and more the composition C₁₅H₂₄ and he, therefore, concludes that the oil of spike contains a hydrocarbon of this formula.

52. Sesquiterpene (?) of Spiraea Oil.

Ettling² obtained a small amount of a hydrocarbon (C₅H₈)_x from the oil, which was either a terpene or a sesquiterpene.

53. Sesquiterpene of Valerian Oil.

By repeated fractionation under diminished pressure, Oliviero³ was able to isolate a sesquiterpene and a sesquiterpene hydrate. The fraction distilling between 160 and 165° under a pressure of 50 mm. agreed fairly well with the formula (C₅H₈)_x. It was laevorotatory -9.2°.

The fraction distilling between 190 and 195°, under the same pressure (50 mm.) agreed fairly well with the formula C₁₅H₂₄H₂O. It was dextrorotatory +2.5° and had the nature of an alcohol as was shown by the formation of a benzoic ester and a hydrochloric acid ester.

In rotatory power this sesquiterpene agrees best with that of caryophyllene, but in the absence of other constants no comparison can be made.

54. Sesquiterpene of Wild Thyme Oil.

The higher boiling fractions of wild thyme oil contain, besides phenols, hydrocarbons, presumably sesquiterpenes,⁴ but there is nothing to warrant this assumption other than the high boiling point.

55. Synthetic Sesquiterpenes.

1 — Methyl — 4 — iso-propyl — 2 — iso — amy l b e n z e n e.
 $(CH_3)_2CH.CH_2CH_2.C_6H_5(CH_3).CH(CH_3)_2$.

Claus⁵ has prepared a synthetic hydrocarbon of the composition C₁₅H₂₄, by reducing isobutyl-p-iso-amyl ketone with iodine and phosphorus to 1-methyl-4-isopropyl-2-iso-amyl benzene. It

¹ Compt. rend., 117, p. 55.

² Ann., 35, p. 243.

³ Bull. Soc. chim., 11, (3), p. 924.

⁴ G.-H.-K., The volatile oils, p. 629.

⁵ Journ. f. prakt. Chem., (2), 46, p. 474; Chem. Centralbl., 1898, I, p. 210.

is a colorless, limpid oil, of faint valerian-like odor, boiling at 245° and having a specific gravity of 0.89 at 17°.

4—Octyl—1—methyl benzene, $C_6H_4(CH_3)C_8H_{17}$.

Lipinski¹ in 1898 prepared this synthetic sesquiterpene according to Fittig's reaction. 17 gr. of *p*-bromtoluene, 24 gr. of octyl-iodide, 7 gr. of sodium, and two to three times the volume of dry ether, were used. The reaction took place after a short time. In order to increase the yield, the mixture was slightly warmed toward the end of the reaction, the ether then distilled off and the product of the reaction fractionated.

This synthetic sesquiterpene is a colorless oil, boiling between 281—283° and solidifies when strongly cooled. The melting point lies between 11 and 12°. Oxidized with a boiling 3 p. c. permanganate solution it yields terephthalic acid, $C_6H_4(COOH)_2$. When treated with fuming sulphuric acid *p*-octyl toluene sulphonic acid, $C_8H_{17}C_6H_3(SO_3H).CH_3$, results, of which the barium (+H₂O), lead (+4H₂O) and copper (+2½H₂O) salts were prepared. With fuming nitric acid it yields mononitro *p*-octyl toluene, $C_8H_{17}C_6H_3(NO_2).CH_3$ and dinitro-*p*-octyl toluene, $C_8H_{17}C_6H_2(NO_2)_2.CH_3$. Treatment with acetyl chloride results in the formation of octyl-tolyl-methyl ketone, $C_8H_{17}C_6H_4(CH_3)CO.CH_3$.

56. Trivalerylene.

In 1867 Reboul² obtained, by treating valerylene with conc. sulphuric acid, an oil from which, after washing and drying, there could be separated by distillation a fraction boiling at 175—177° corresponding to the formula $C_{10}H_{16}.H_2O$, and a hydrocarbon $C_{15}H_{24}$ boiling between 265—275°, and having a specific gravity of 0.862 at 15°. Diluted sulphuric acid has a similar action on valerylene.

By heating valerylene in sealed tubes to 250—260° Bouchardat³ in 1878 obtained a hydrocarbon $C_{10}H_{16}$ and an other $C_{15}H_{24}$. The latter compound boiled between 240—250° and gave a monochlorhydrate which was decomposed by heat.

57. Vetivene.

Gladstone⁴ in 1872 obtained from oil of vetiver, by destroying

¹ Ber., 31, p. 940.

² Compt. rend., 64, p. 419; Ann., 148, p. 373.

³ Compt. rend., 87, p. 654; Bull. Soc. chim., 33, p. 24.

⁴ Journ. Pharm., 81, pp. 687, 705.

the oxygenated constituents by means of sodium, a small amount of a rather viscid hydrocarbon, of the following properties:

B. p. 255°; $d = 0.9332$; $N_A = 1.5061$.

Gladstone did not have this compound, which he considers to be a sesquiterpene, in a pure condition.

Genvresse and Langlois¹ separated from oil of vetiver a sesquiterpene by fractional distillation and three rectifications from sodium. To this fraction they gave the name of vetivene. It is a colorless, mobile liquid of the following properties: $d_{20}^{\circ} = 0.932$; $a_{D15}^{\circ} = +18^{\circ}19'$; b. p. 135° (15 mm.), 262–263° (740 mm.).

It absorbs four atoms of bromine, without disengaging hydrobromic acid; the liquid is colored blue.

Vetivenol, $C_{15}H_{26}O$, also found by Genvresse and Langlois, has the following properties: $d_{20}^{\circ} = 1.011$; $a_D = +53^{\circ}43'$ in alcoholic solution; b. p. 169–170° (15 mm.).

According to these chemists dehydrating agents give rise to a sesquiterpene of the general properties of vetivene.

58. Winterene.

By the action of sodium on the oil obtained by steam distillation from Winter's bark and subsequent fractionation, Arata and Canzonari² obtained the following fractions; 1. –250°; 2. 250–260°; 3. 260–270°; 4. 270–280°. Fraction 260–270° had the sp. gr. 0.9344 at 13°. The original oil was dextrogyrate and fraction 255–270° showed a rotation of +11.2°. Fraction 260–265° made up the bulk of the oil and was called by them winterene. The index of refraction of this fraction was 1.4931. It had the composition C_5H_8 , and in accordance with the vapor density 11.67 the authors gave to winterene the formula $C_{25}H_{40}$. This is doubtful, as the compound readily absorbs oxygen from the air. Moreover, the boiling point is rather low for so complex a substance, corresponding rather with that of the sesquiterpenes. With hydrochloric acid it yields a liquid addition product having a camphoraceous odor. The chemical work done on this substance is meagre, being restricted almost entirely to color reactions. The subject seems well worthy of further

¹ Compt. rend., 135, p. 1059.

² Anales de la Cientifica Argentina; Drugg. Bull., 1889, p. 140; Arch. d. Pharm., 227, p. 818; Jahresb. f. Pharm., 1889, p. 70; Pharm. Ztg., 1889, p. 388.

investigation in the light of the more recent work on the sesquiterpenes.

59. Zingiberene.

General Discussion and History.

Zingiberene has so far been found only in ginger oil. The first investigation of ginger oil was made by Papousek¹ in 1853, who did not, however, recognize the sesquiterpene. Thresh² in 1881 found the major portion of the oil to consist of a sesquiterpene boiling between 256–260°. This fraction had a specific gravity of 0.899 and a rotatory power of –16.10°. Nitroso derivatives of the sesquiterpenes were unknown at that time, so that Thresh was limited in his investigation to the attempt to prepare a hydrochloride, which failed.

In 1900 v. Soden and Rojahn³ published the results of an examination of the sesquiterpene of ginger oil. It had a specific gravity of 0.872 at 15° and a rotation of –69°. By titration with bromine in glacial acetic acid solution, they determined the presence of two ethylene bonds. The tetrabromide formed could not be obtained in a crystalline condition. The hydrochloric acid and hydrobromic acid addition products are reported as brown, viscous oils. Attempts to prepare a nitrosochloride and a nitrosate failed.

The physical properties, specific gravity and rotatory power of this sesquiterpene did not agree with any of the known sesquiterpenes, and v. Soden and Rojahn, therefore, proposed the name of zingiberene for the sesquiterpene.

Schreiner and Kremers⁴ published their results obtained with zingiberene somewhat later. While the physical constants found by them agree in the main with those of v. Soden and Rojahn, their chemical results are different as they succeeded in preparing a dihydrochloride, a nitrosochloride, a nitrosate and a nitrosite, thus definitely characterizing this sesquiterpene.

The low specific gravity of zingiberene is striking, and it, together with its molecular refraction indicate the presence of more double bonds and less cycles than are present in most other sesquiterpenes. The molecular refraction of zingiberene speaks strongly for three double bonds but its chemical derivatives so far prepared

¹ Journ. Pharm. Chim., (8), 28, p. 465.

² Pharm. Journ., (8), 12, p. 248.

³ Pharm. Archives, 4, pp. 61, 155.

are not concordant. Thus, for instance, it forms a well crystallized dihydrochloride. This disagreement is similar to that which existed in the case of caryophyllene, but later chemical work confirmed the optical method. The optical method is probably the most trustworthy in this case, for the following reasons:

1. The optical method has proven trustworthy in the case of caryophyllene and with a large number of compounds in other fields of research. The argument that the zingiberene subjected to the optical test was not absolutely pure, being obtained by fractional distillation, while true, has but little bearing on this question. The properties of the ginger fractions, show that those immediately preceding and following the zingiberene fraction are higher in specific gravity than the zingiberene. Any admixture with these would, therefore, increase the specific gravity of the zingiberene. It is, however, the very low specific gravity of this compound which causes the result to come out for three double bonds. The specific gravity is a far more sensitive factor in the formula $\frac{n^2-1}{n^2+2} \cdot \frac{m}{d}$ than is the index of refraction.
2. The sesquiterpene has a much lower specific gravity than the sesquiterpenes with only two double bonds. This is, however, a change concomitant with the introduction of double bonds, the composition remaining unchanged.
3. It is almost always far more difficult to form a tri-derivative than a mono- or di-derivative. The dihydrochloride would of course, form first, and being a crystalline compound, may separate out. The tri-hydrochloride would form with much greater difficulty, if indeed it can be formed at all. Moreover, an inversion with the production of an isomeric sesquiterpene, as occurs evidently in the preparation of caryophyllene hydrate, and which is also discussed under cadinene and its dihydrochloride, is not excluded. In the bromine titration, hydrobromic acid is given off, so this method of testing for the number of double bonds becomes untrustworthy.

Further work is necessary before this question can be definitely decided.

Preparation.

Zingiberene is obtained by the fractional distillation of ginger oil. v. Soden and Rojahn fractionated the oil under a pressure of 8–10 mm. The portion going over at 120–125° was saponified

with alcoholic potash and the washed oil again fractionated in a vacuum. Schreiner and Kremers³ proceeded in a similar manner, collecting fraction 150–160° (32 mm.), saponifying this and again fractionating, collecting fraction 160–162°.

Physical Properties.

The physical constants of zingiberene are as follows:

Thresh (1881): B. p. 256–260°; $d = 0.899$; $\alpha_D = -16.10^\circ$.

v. Soden and Rojahn (1900): B. p. 134° (14 mm.); 269–270° (760 mm.); $d_{15} = 0.872$; $\alpha_D = -69^\circ$.

Schreiner and Kremers (1901): B. p. 160–161° (32 mm.); $d_{20} = 0.8731$; $[\alpha]_D = -73.38^\circ$; $n_D = 1.49399$.

The molecular refraction was 67.87; the calculated molecular refraction, assuming three double bonds, is 67.86.

Schreiner and Kremers also determined the indices of refraction from the three hydrogen lines. They were as follows:

$$H\alpha = 1.49041. \quad H\beta = 1.50319. \quad H\gamma = 1.51112.$$

Zingiberene is a colorless, mobile liquid, but readily resinifies and becomes viscous. It is readily soluble in ether, petroleum ether, benzene and absolute alcohol, more sparingly (1:16) in ordinary alcohol.

Chemical Properties.

Zingiberene readily absorbs oxygen from the air. Bromine combines with it, but as hydrobromic acid is formed, no bromide could be obtained. With hydrochloric acid it combines to form a dihydrochloride, and with nitrosylchloride and the oxides of nitrogen to form a nitrosochloride, a nitrosoite and a nitrosate respectively.

Zingiberene dihydrochloride, $C_{15}H_{24} \cdot 2HCl$. Thresh⁴ in 1881 attempted to prepare the hydrochloride by passing the dry gas into an ethereal solution of the sesquiterpene fraction, but no crystalline compound could be obtained. Thresh attempted to remove the excess of hydrochloric acid by heating in a current of dry hydrogen until the escaping gas no longer reddened moistened blue litmus paper. The result was unsatisfactory, as analysis showed only 5.47 p. c. of HCl, corresponding to the improbable formula $(C_{15}H_{24})_3HCl$. The specific gravity of this liquid was 0.9246.

³ Pharm. Archives, 4, p. 155.

⁴ Pharm. Journ., (8), 12, p. 245,

Von Soden and Rojahn report the hydrochloric acid addition product as a brown viscous oil but Schreiner and Kremers⁵ obtained this derivative in a crystalline form. It is prepared as follows:

Zingiberene is dissolved in an equal volume of glacial acetic acid and the solution saturated with dry hydrochloric acid gas at 0°. The solution is then allowed to stand for a day or two, after which time the dark colored liquid will be found to be interspersed with fine needles. These are collected on a force filter and washed with cold alcohol. A second crop can usually be obtained by again saturating the mother liquor with dry hydrochloric acid gas. When recrystallized from hot alcohol, the dihydrochloride is pure white and melts at 168—169°.

Zingiberene nitrosochloride. Schreiner and Kremers prepared this as follows:

A small portion of zingiberene is dissolved in an equal volume of glacial acetic acid and of ethyl nitrite. After cooling in a freezing mixture, it is gradually treated with twice the volume of zingiberene used, of a saturated solution of hydrochloric acid gas in glacial acetic acid. After a minute or two the reacting mixture is treated with twice its volume of alcohol, continually agitating. The nitrosochloride separates out as a flocculent precipitate. This is collected on a force filter and well washed with cold alcohol. It is a fine white powder, and may be purified by dissolving in ethyl acetate and precipitating with alcohol. Thus obtained, it melts at 96—97° with decomposition.

Zingiberene nitrosate. This derivative does not separate when the hydrocarbon is treated in the usual manner, but with a slight modification it separates in large quantities, the yield being almost theoretical. The procedure is as follows:

A small portion of zingiberene is dissolved in an equal volume of glacial acetic acid and of ethyl nitrite. This mixture is well cooled in a freezing mixture and then treated slowly with a mixture of nitric acid and glacial acetic acid, each equal in volume to the zingiberene used. The first few drops produce a deep bluish-green color which rapidly fades. The mixture remains clear but becomes quite thick, and toward the end of the reaction turbid and exceedingly viscous. At this stage the mixture is treated with about four times its volume of cold alcohol, and on shaking, large quantities of the

⁵ Pharm. Archives, 4, p. 161.

nitrosate separate. This is collected on a force filter, washed with alcohol and dried on a porous plate. Attempts to purify the product by crystallization have so far been unsuccessful. The compound may be purified by dissolving in ethyl acetate and precipitating with alcohol. It is a slightly yellowish powder melting at 86-88° with decomposition.

Zingiberene nitrosite. This derivative is more readily obtained than the other nitroso-compounds of this sesquiterpene. It can be obtained in a pure state with comparative ease if the recrystallization is done on a small quantity and with but a momentary application of heat. When so purified its melting point is sharp and the compound is, therefore, well suited for identifying the sesquiterpene. Schreiner and Kremers prepared this derivative as follows:

A small portion of zingiberene is dissolved in about 10 times its volume of petroleum ether and is then cooled in ice water or a freezing mixture. It is then treated with a volume equal to the zingiberene used, of a saturated solution of sodium nitrite, and the same amount of glacial acetic acid. The liquid shows a passing blue color and on shaking solidifies completely to a mass of white crystals. The magma is best transferred to a cloth and washed with cold water and pressed. After spreading on a porous plate for a short time the compound must be purified at once, as it readily decomposes when in an impure condition. This is best done by recrystallizing from hot methyl alcohol, working with small portions at a time and avoiding heating for any length of time. If heated for only a few moments crystals will be obtained. Even a momentary heating will result in considerable loss, but the crystals which separate are fine silky needles, and after washing are quite pure. If thought necessary the operation may be repeated. Thus purified the compound melts at 97-98°. It is much less stable than the corresponding caryophyllene compound. After keeping for a few weeks it becomes yellow and soon changes to a black, sticky mass.

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